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Peush Sahni
Sujoy Pal *Editors*

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Volume 26

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Series Editor

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This compendium of reviews in gastrointestinal surgery covers topics that are of contemporary interest to surgeons reflecting the popular trends in this field. Started by the *Indian Association of Surgical Gastroenterology* (IASG), the GI Surgery Annual has covered a journey of over 2 decades which speaks for its relevance and popularity among general and gastrointestinal surgeons. The reviews contain up-to-date scientific content of enduring academic interest with each new volume covering 10-12 topics. From 2016 onwards, this Annual turns a new page in its academic journey by publishing the forthcoming titles with Springer. The editorial control continues to remain with the IASG and the current editorial board.

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Peush Sahni • Sujoy Pal
Editors

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Editor-in-Chief T. K. Chattopadhyay

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Chapter 1
Total Pancreatectomy and Islet Autotransplantation for Chronic Painful Pancreatitis

Megan Berger, David E. R. Sutherland, and Srinath Chinnakotla

1.1 Introduction

Chronic pancreatitis (CP) is an often painful and debilitating disorder that remains a challenge for both patients and physicians. It is a rare disorder, with an estimated incidence of 0.2%–0.6% in the USA [1, 2]. Despite its rarity, the economic impact of CP is substantial, with total estimated annual healthcare expenditure of US$ 2.6 billion [3]. Frequent hospital admissions, emergency department visits and lost days of work become a tiresome and expensive way of life for patients with recurrent or constant pain due to CP. Additionally, if left untreated, many patients will develop exocrine and endocrine insufficiency, and some will go on to develop pancreatic cancer [4, 5].

The goal of treating CP is to reduce pain and restore quality of life. Initial interventions are aimed at correcting the mechanical, metabolic, immunological or pharmacological causes of the disease. Medical options can include antioxidants, pancreatic enzymes (which both reduce pancreatic stimulation and treat pancreatic exocrine insufficiency), narcotic analgesics and nerve block procedures [6, 7]. Endoscopic interventions may include stone extraction, sphincterotomy, stricture dilation and stent placement [6, 8]. If medical or endoscopic treatments are not successful, patients may be candidates for surgery.

Surgical techniques include partial pancreatic resection (Whipple or distal pancreatectomy) and drainage procedures such as lateral pancreaticojejunostomy (Puestow) and variants (Frey, Beger). Patients often have transient pain relief, but due to the diffuse and progressive nature of CP, pain eventually recurs in up to 50%

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of patients [9, 10]. Furthermore, patients frequently continue to develop exocrine and endocrine insufficiency despite surgery [11–14].

A total pancreatectomy (TP) completely removes the root cause of the pain in chronic pancreatitis. The diseased gland is excised completely, and, unlike with partial resections or surgical drainage procedures, there is no potential for pancreatic duct leakage [15]. Performed in isolation, without preservation of any beta-cell function, a TP would result in brittle surgically induced diabetes with the added problem of exocrine pancreatic insufficiency. However, when combined with an intraportal islet autotransplantation (TP-IAT), beta-cell mass can be preserved following TP allowing for insulin secretory capacity and reduction of diabetic symptoms and complications.

The world's first TP-IAT was performed at the University of Minnesota in 1977 to treat a patient with painful CP [16]. She was pain-free and insulin-independent for 6 years, when she died of unrelated causes [17]. Since then, outcomes following TP-IAT have been generally favourable, with the vast majority of patients reporting improved pain and quality of life and many patients requiring little to no insulin to manage postoperative diabetes. With these favourable outcomes, the procedure has gained increasing acceptance as a treatment for CP. Presently, there are over 20 centres worldwide with active TP-IAT programmes, and over 1000 of these procedures have been reported in the literature [18–30].

1.2 Evaluation and Selection of Patients

Due to the extensive nature of the operation and the potential complications of insulin dependence, gastrointestinal dysmotility and post-splenectomy infection, patients must be selected with considerable care. Criteria for selection of patients for TP-IAT have evolved over time. Table 1.1 summarizes the selection criteria used at the University of Minnesota. Generally, the patient must meet diagnostic criteria for chronic or acute relapsing pancreatitis, have pain that is consistent with pancreatitis despite previous medical and/or endoscopic procedures and have significant impairment in quality of life as a result of pain. The decision to offer a TP-IAT is made by a multidisciplinary team consisting of gastroenterologists, surgeons, endocrinologists, pain specialists, health psychologists, dietitians and nurse coordinators. All patients and families must receive information on the use of pancreatic enzyme supplementation, the risk of insulin-dependent diabetes, the risk of post-splenectomy infection, the likelihood of long-term pain relief and any other available therapeutic options. Patients also undergo psychological and pain evaluations. Those found to have complex substance abuse issues or having difficult pain management regimens may be offered additional approaches for anxiety, chemical dependency and pain management prior to consideration of TP-IAT.

TP-IAT should not be offered to patients with active alcoholism or illegal drug usage, poorly controlled psychiatric illness or anticipated inability to comply with the complicated postoperative regimen [31]. Additionally, patients with pancreatic

Table 1.1 Criteria for a TP-IAT, University of Minnesota

Definitions

Chronic pancreatitis (CP)

Chronic abdominal pain, lasting more than 6 months; features consistent with CP; and evidence of CP by at least one of the following:

1. Morphologic or functional evidence of CP [per computed tomography (CT) of the abdomen indicating calcifications, or per endoscopic retrograde cholangiopancreatography (ERCP)].
2. At least six of nine criteria positive for CP per endoscopic ultrasound (EUS).
3. At least two of the following:
   (a) Findings suggestive of CP (abnormal duct or side branch) per secretin-enhanced magnetic resonance cholangiopancreatography (sMRCP) or.
   Magnetic resonance imaging (MRI) T1 evidence of fibrosis
   (b) At least four of nine criteria positive for CP per EUS.
   (c) Abnormal exocrine pancreatic function test results (peak bicarbonate <80).

or

Relapsing acute pancreatitis (relapsing AP):

1. Three or more episodes of documented AP (elevated amylase or lipase, CT evidence) with ongoing episodes for more than 6 months, and with disabling interval pain similar to AP pain.
2. No evidence of current gallstone disease (patients with gallstones should undergo a cholecystectomy) and no evidence of other correctable conditions such as AP.

or

Documented hereditary pancreatitis with compatible clinical history

Indications for a TP-IAT (must have all of below):

1. Documented CP or relapsing AP with chronic or severe abdominal pain, directly resulting in at least one of the following:
   (a) Chronic narcotic dependence (narcotics required on a daily or near-daily basis for >3 months).
   (b) Impaired quality of life (QOL), per the RAND medical outcomes study 36-item short form (SF-36) health survey.
2. Complete evaluation with no reversible cause of CP or relapsing AP present or untreated.
3. Unresponsiveness to maximal medical therapy and endoscopic therapy.
4. Ongoing abdominal pain requiring routine narcotics for CP or relapsing AP.
5. Adequate islet function (i.e. either no diabetes or non-insulin-requiring diabetes with positive C-peptide levels).

Contraindications for a TP-IAT

- Active alcoholism (to be considered for a TP-IAT, patient must be abstinent for 6 months with documented success of therapy).
- Pancreatic cancer.
- End-stage pulmonary disease, cirrhosis or severe arteriosclerotic heart disease.
- Poorly controlled psychiatric illness.
- Inability to comply with postoperative regimen.
- Intraductal papillary mucinous neoplasia (patient should undergo an IAT only as part of a clinical trial).
- Illegal drug usage (to be considered for a TP-IAT, patient must be abstinent for 6 months with documented success of therapy).

malignancy, cirrhosis, portal vein thrombosis, portal hypertension, high-risk cardiopulmonary disease or C-peptide-negative diabetes are not considered eligible for the procedure [30, 31]. TP-IAT has been performed in the presence of benign pancreatic tumours by some centres [32–35].

Chronic pancreatitis has been shown to increase patients' risk of pancreatic adenocarcinoma; approximately 5% of patients with CP developing carcinoma over a period of 20 years [36]. The risk is even greater in patients with hereditary pancreatitis, approaching 40%–55% in the same time period [36]. Currently, no formal guidelines exist for screening potential TP-IAT patients for pancreatic adenocarcinoma. Certainly, these patients undergo extensive imaging during the course of their disease prior to TP-IAT. If radiographically suspicious lesions are identified on imaging, the possibility of malignancy should be investigated, noting that serological biomarkers are minimally helpful in distinguishing early cancer from chronic pancreatitis [37].

There is a theoretical risk that patients after TP-IAT could develop pancreatic cancer in transplanted cells within the liver. Investigators in Minnesota have reported that they have not seen any cancer in the liver in a cohort of 484 patients with 2936 person years of follow-up [38]. This does not, however, rule out the possibility.

1.3 Surgical Procedure

The surgical technique for TP-IAT has evolved over decades and has been described in detail elsewhere [30, 39]. Briefly, the pancreas is removed along with the C loop of the duodenum and distal bile duct, followed by gastrointestinal reconstruction. A duodenum-preserving operation has been described, but was associated with duodenal ischaemia and thus has fallen out of favour [17, 26, 40]. A cholecystectomy is always done, and an appendectomy is often included in the procedure if not previously performed.

The decision to perform a splenectomy is institution, surgeon and patient-dependent [23, 40, 41]. Spleen-sparing total pancreatectomy is feasible in many cases and allows patients to avoid potential post-splenectomy infections [30, 40]. However, spleen preservation may be technically difficult due to severe fibrosis, calcification, pseudocyst or haemorrhage [40]. Additionally, spleen preservation carries the risk of splenic congestion with gastric varices, ischaemia, infarction, intrasplenic collections and portal vein thrombosis, all of which may require reoperation [40, 41]. The authors' preference is to always perform a splenectomy as part of TP-IAT.

The critical element of the procedure is the preservation of blood supply to the pancreas until just before its removal. This decreases warm ischaemia time and maximizes islet preservation. Following resection, the pancreas is immediately placed in cold balanced electrolyte solution for transport to the islet laboratory. Gastrointestinal reconstruction is completed while the pancreas is being processed in the islet laboratory. This can be accomplished with a choledochojejunostomy along with either a duodenoduodenostomy or duodenojejunostomy.

Duodenojejunostomy with Roux-en-Y configuration is preferred by some surgeons in order to avoid the complication of bile reflux (Fig. 1.1a and b) [39]. A nasojejunal feeding tube is routinely placed to allow for postoperative gastric decompression and jejunal tube feeding.

Recently, TP-IAT has been performed using the minimally invasive approach [42].

1.4 Islet Isolation and Infusion

The method of islet isolation has remained the same with minor modifications throughout the years. The process involves dispersion of the pancreas in a series of steps, which are variable across institutions. First, a collagenase solution is injected into the main duct to distend the pancreas and enzymatically disrupt the exocrine

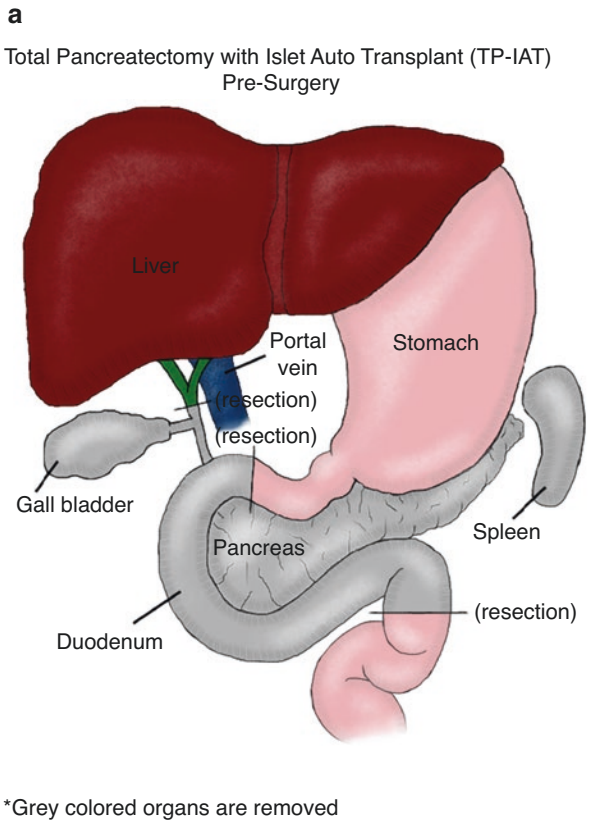

Fig. 1.1 Reconstruction: Roux en Y choledochojejunostomy, duodenojejunostomy (**a** and **b**)

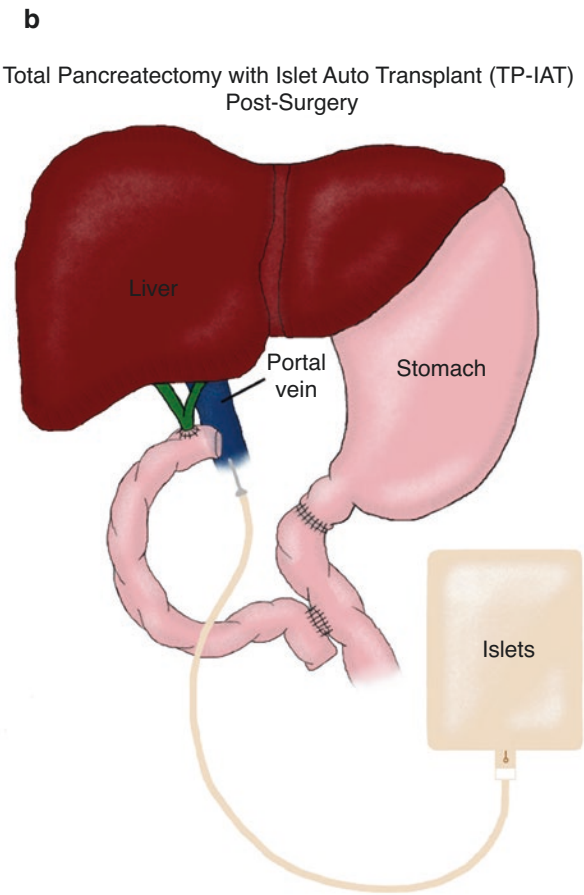

Fig. 1.1 (continued)

pancreas (sparing the islets) [43]. Next, digestion in a shaking (Ricordi) chamber is performed at 34°–37 ° C to mechanically disperse the pancreatic tissues [44].

After digestion, the islets are generally infused as an unpurified preparation in order to retain the greatest number of islets possible. Purification is reserved for select cases when a large volume of pancreatic digest (≥0.25 ml/kg patient body weight) is obtained [45–47]. The final islet tissue preparation is suspended in culture medium with human serum albumin, buffering solution, antibiotic and heparin to protect against aggregation before infusion.

Heparin is administered prior to islet infusion, most commonly with an initial bolus of 70 units/kg body weight [46]. Islets are infused into the portal system over a period of 30–60 minutes, typically through a cannula inserted into the splenic vein stump. Portal pressures are monitored, and the infusion is stopped if any of the following criteria are met: the total tissue volume exceeds 0.25 ml/kg, the intraportal

pressure exceeds 25 cm H_2O, or the portal blood flow decreases to less than 100 ml/minute when measured by an electromagnetic flow meter. Any remaining islets are then implanted at an alternate site, such as intraperitoneal, beneath the renal capsule, or the submucosal layer of the stomach [48]. No matter the site, the islets initially survive by nutrient diffusion until neovascularization occurs [49, 50]. During this time, the islets are minimally functional and are susceptible to environmental stress [41].

1.5 Early Postoperative Care

After islet infusion, patients are placed on a heparin drip or *low molecular weight heparin* to minimize the risk of portal vein thrombosis. Portal vein thrombosis remains a risk in the days following islet infusion [51]. As such, surveillance by Doppler ultrasound has been recommended during the immediate postoperative period. If discovered to have a portal vein thrombus, the patient is prescribed a 3-month course of warfarin [52].

Patients are routinely given intravenous narcotic analgesics in the period immediately following TP-IAT. Notably, use of a dexmedetomidine infusion and *paravertebral* nerve blocks can augment early postoperative pain control and reduce narcotic analgesia needs [53–56]. After conversion to oral analgesics, patients are weaned off these medications gradually, most often in the outpatient setting in collaboration with their local providers.

Return of gastrointestinal motility and function is often delayed postoperatively. With a nasogastric tube in place, symptomatic relief from gastroparesis can be accomplished by decompression. Enteral feeds are initiated early postoperatively. Pancreatic enzymes are added to the tube feed formula to compensate for the patient's complete exocrine insufficiency. As delayed gastric emptying improves, oral diet is reintroduced and tube feed volume is reduced. All patients are educated on use of pancreatic enzymes, starting with 1000 lipase units/kg/meal and advancing to a goal of 1500 units/kg/meal. Fat-soluble vitamin supplementation is recommended and serum vitamin levels are monitored for life [57].

Autotransplanted islets are not capable of full function immediately following infusion. During recovery and engraftment, tight glucose control is necessary to protect against beta-cell functional stress [58]. As such, patients are started on an insulin infusion immediately following TP-IAT. Once a stable tube feeding regimen is established, patients are transitioned to subcutaneous insulin. Use of exogenous insulin continues for at least 3 months while engraftment of the islets takes place. Thereafter, insulin can be weaned off if blood glucose levels remain in a near-normal target range, indicated by fasting blood glucose of <125 mg/dl, postprandial glucose <180 mg/dl and glycated haemoglobin of ≤6.5% [30]. Outside of those ranges, patients must be maintained on insulin.

Patients are followed up multiple times in the first year after TP-IAT. Labs and follow-up appointments are recommended at 3 months, 6 months, 1 year and then annually. Laboratory studies at these intervals include fasting glucose and C-peptide, stimulated glucose and C-peptide and haemoglobin A_{1c} level.

It has become routine at our institution to distribute quality of life surveys to patients undergoing TP-IAT before surgery and again at 3 months, 6 months, 1 year and then annually [59]. The surveys include the RAND Medical Outcomes Study 36-item Short Form (SF-36) health survey as well as additional questions about narcotic use, pain symptoms, 'pancreatic pain' (whether or not it was similar to preoperative levels) and insulin requirements [59].

1.6 Surgical Complications

The in-hospital mortality following TP-IAT has been reported as 0%–2% [23–26, 30, 60]. Surgical complications requiring reoperation under general anaesthesia have been reported at a rate of 4.4%–15.9% of patients [26, 30, 60–63]. These complications include bleeding, anastomotic leaks (both biliary and enteric), intra-abdominal abscess, bowel obstruction or ischaemia, wounds requiring debridement and splenic bleeding or ischaemia in patients with spleen-preserving TP-IAT [26, 30]. A subset analysis of patients with postoperative bleeding revealed that patients with post-infusion portal pressures >25 cm H_20 have a higher risk of postoperative bleeding (15% vs. 7.4%) [30].

A recent study using the National Surgical Quality Improvement Program (NSQIP) data compared TP-IAT with TP alone and noted that the IAT is associated with greater risk of major perioperative morbidity (41% vs. 28%) and blood transfusion (20% vs. 7%) as well as a longer hospital stay (13 days vs. 10 days) [64]. There was no difference in mortality or minor morbidity. Notably, this study did not include any follow-up data after discharge and could not comment on long-term outcomes related to glycaemic control. While the short-term morbidity appears to be higher in TP-IAT patients than TP patients, this must be weighed against the morbidity of inevitable pancreaticogenic diabetes resulting from TP alone.

1.7 Islet Function

Islet function after TP-IAT is variable among patients. Patients are classified as either (i) insulin-independent, (ii) partial graft function (stimulated C-peptide ≥0.6 ng/dl or, if C-peptide unknown, the ability to maintain target glucose levels using only long-acting insulin or with only rare short-acting insulin) or (iii) insulin-dependent (stimulated C-peptide <0.6 ng/dl or need for daily short-acting insulin) [30]. The most important predictor of insulin independence is islet yield at the time

of operation [30]. Islet yield is negatively affected by prolonged duration of disease, previous pancreas surgery (especially lateral pancreaticojejunostomy) and alcoholic aetiology [22, 25, 28, 31, 65, 66].

Overall, patients achieve insulin independence at a rate of 19%–40% at 1 year [23, 24, 30, 62, 67]. Of patients with yields of >5000 IEQ/kg, greater than 70% are insulin-independent at 3 years, highlighting the importance of maximizing islet yields [30]. Those who attain insulin independence must continue to be monitored for diabetes since attrition over time has been reported by multiple institutions [23, 30].

Importantly, the majority of patients who undergo TP-IAT demonstrate some degree of islet function, thus minimizing the severity of their diabetes and associated complications. In the Minnesota series, 49% of patients had partial graft function at 1 year based on the criteria listed above, meaning only 23% were considered insulin-dependent [30]. Several other institutions classify islet function based on daily insulin requirements. For instance, in a recent Cincinnati series, 38% of patients required fewer than 20 units daily and were thus classified as partial graft function [23]. In a series from Leicester comparing TP-IAT to total pancreatectomy alone, the group receiving islets had a significantly lower daily insulin requirement at 22 i.u. compared with 35 i.u [68].

Once successfully engrafted, autotransplanted islets appear to function similar to native islets. Dynamic assessments of beta- and alpha-cell secretion stimulated by intravenous arginine and glucose show that both intrahepatic cell types function normally in terms of magnitude and timing of secretion [69]. More robust insulin secretion is seen in patients with higher islet mass transplanted.

1.8 Quality of Life

The Rand Corporation SF-36 is a survey which measures health-related quality of life (HRQOL) and has been used at multiple institutions to assess patients before and after TP-IAT [23–25, 30, 70, 71]. Overall, before TP-IAT, patients show below-average HRQOL scores compared with the standardized American population, with mean Physical Component Scale (PCS) and Mental Component Scale (MCS) scores at 2 and 1.5 standard deviations lower than average [30, 63]. After surgery, scale scores for all 8 of SF-36 health dimensions, including PCS and MCS, have been repeatedly shown to improve [23, 25, 30, 71]. Additionally, 85%–91% of patients report overall improvement in their health at 1 year after TP-IAT [23, 30]. These results have shown durability; SF-36 surveys at 5 years and beyond (range 60–132 months) demonstrating persistent improvements in all subscales from baseline values [23]. Importantly, patients with daily insulin requirements also show significant improvements in HRQOL, though the degree of improvement in this group has been variable across institutions [30, 70].

1.9 Pain Resolution

Patients undergo TP-IAT to alleviate pain, which makes postoperative pain control a critical outcome to assess. Prior to undergoing TP-IAT, most patients have been on narcotics for several years, with a mean duration of 3.6 years [30]. In the Minnesota series, daily or intermittent narcotic use decreased from 100% of 207 patients preoperatively to 91%, 61%, 54% and 51% of patients over 3, 6, 12 and 24 months postoperatively [30]. Similar results have been reported from other institutions. Cincinnati reports 55% narcotic independence at 1 year, with improvement to 73% independence at 5 years [23]. Arizona has reported that 71% of patients are 'pain-free' and off narcotics at 1 year [24]. Regardless of narcotic use, 94% of patients in the Minnesota study stated their pain had improved at 1 year [30].

Those who continue to report pain following pancreatectomy present a perplexing issue since the original source of their pain has been removed. In a recent analysis of >500 patients, independent risk factors for 'pancreatic pain' at 1 year were pancreas divisum and hereditary causes of CP, body mass index >30 and a high number of previous stents (>3) [72]. It has been postulated that such pain stems from irreversible maladaptive central pain pathways that develop over the duration of CP [42, 63]. Postoperative gastrointestinal motility disorders may play a role as well [73].

1.10 Conclusions

TP-IAT is an effective treatment for patients with debilitating chronic pancreatitis that is refractory to other treatments. Utilization of TP-IAT in the treatment of CP has steadily increased over the past 3 decades and can offer pain relief, narcotic independence and improved quality of life to recipients. TP-IAT preserves some degree of islet function in majority of patients, minimizing the burden of surgical diabetes. Additionally, TP-IAT has also been shown to be an effective cost-saving strategy over more conservative measures in patients with severe CP [60]. While these successes are encouraging, TP-IAT continues to present major challenges of long-term diabetes, pancreatic exocrine insufficiency, potential surgical complications and occasional difficulty with narcotic weaning. Careful patient selection remains paramount.

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Editorial Comment
Both chronic pancreatitis and recurrent acute pancreatitis are progressive diseases in which the gland is replaced with extreme fibrosis causing destruction of pancreatic parenchyma resulting in deficiencies of exocrine and endocrine functions. The unfortunate victims suffer from intractable abdominal pain, diabetes, exocrine deficiency with poor quality of life, necessitating frequent

hospital visits, loss of work and increased healthcare costs. Conventionally these patients are first managed conservatively with diet modification (low fat content) and pancreatic enzymes to reduce pancreatic stimulation. Simultaneously they are provided pain-alleviating measures. Selected patients are managed with endoscopic measures (sphincterotomy and stenting) when these measures fail; they are subjected to pancreatic ductal drainage or pancreatic parenchymal resection; unfortunately, results of these are not entirely satisfying. Such patients, particularly those with small duct disease or with genetic form of the disease, are now increasingly being offered total pancreatectomy and islet autotransplantation (TP-IAT).

The operation is a two-dimensional one. Total pancreatectomy is aimed at relieving pain, and islet transplantation is directed to control diabetes. With this, studies have shown improvement in pain (either totally free or with significantly reduced use of analgesics) and better quality of life. Poor pain control has been reported to be related to alcoholic aetiology, prolonged use of narcotics and predominately central pain processing. It is worthwhile to note that paediatric patients have better pain control. They even have more insulin-free life. In adults, control of diabetes is variable; while 30–50% of patients become insulin-independent, others continue to require insulin. The latter situation is related to low islet cell yield or poor engraftment of infused islet cells [1–3].

The above discussion brings us to the question how to improve results of TP-IAT further. Patient selection, identification of the right disease/patient (small duct disease, alcohol abuse, prolonged pre-surgery opioid use, long duration of disease, etc.), these aspects have not been adequately addressed as yet. Similarly, timing of TP-IAT has to be decided. This is important because the longer the duration of the disease, the greater is the islet cell loss which may be the reason for poor diabetes control. To improve results of TP-IAT, what is needed is to organize multicentre study for better patient selection and deciding optimal timing of the procedure. It is equally important to assess quality of life after the operation. It goes without saying that the cost efficacy too needs to be addressed because apart from the operation itself, the instruments used for pancreatic digestion, islet isolation and infusion as of now are quite expensive.

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Chapter 2
Cholangiopancreaticoscopy: A Distinct Diagnostic and Therapeutic Tool in the Current Era

Sumit Bhatia, Sukrit Sud, and Randhir Sud

2.1 Background

Direct visualization of the bile duct and pancreatic duct using per-oral endoscopes has always been a challenging frontier for endoscopists since a long time. Per-oral cholangioscopy (POCS) using miniature endoscope, through the channel of a standard duodenoscope, was first described more than 40 years ago in the 1970s [1, 2]. The procedure never became popular because of fragile instruments, poor image quality, prolonged procedure time and the need for two trained endoscopists.

Over the past two decades, technological advancements have overcome many of these issues, and per-oral cholangiopancreaticoscopy (POCPS) or direct cholangioscopy, as it is popularly known, is fast establishing itself as an indispensable tool for pancreatico-biliary diseases [3, 4]. This article reviews the basic concepts of cholangioscopy, its utility and current status in literature.

2.2 Equipment and Techniques

Cholangioscopy can be done using video endoscope-based systems, which are the traditional 'mother–baby' scopes, or the commonly used catheter-based systems (SpyGlass, Boston Scientific). The above-mentioned systems are classified under indirect per-oral cholangioscopy (iPOC) methods, as the visualization is retrograde as in ERCP.

In patients with dilated bile ducts, direct per-oral cholangioscopy can be done using ultra-slim endoscopes.

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2.3 Video Cholangioscope: Mother–Baby Systems

These systems comprise of a standard mother duodenoscope; through the accessory channel of this mother scope, a miniature daughter or baby cholangioscope is passed inside the bile duct [5]. The daughter scope is an ultra-slim video cholangioendoscope (CHF-B260; Olympus, Tokyo, Japan) with an outer diameter of 3.4 mm. This scope is passed through the accessory channel (4.2 mm) of regular duodenoscope (Fig. 2.1) [6, 7].

The baby scope or cholangioscope has an accessory channel of 1.2 mm, which is used for irrigation during the imaging. The whole system requires two endoscopists, one each for operating the mother and baby endoscopes, respectively. The insertion of the baby scope into the bile duct is facilitated by doing a papillotomy. The cholangioscope is then inserted into the duodenoscope channel usually over a guidewire, and is advanced into the bile duct using the elevator. This is the crucial procedural step as the chances of damage to the tip of cholangioscope are maximum here. The use of a guidewire usually minimizes this damage [6, 7].

The primary shortcomings of these systems were the need for two trained endoscopists, fragile instruments, the cost of the endoscopes, lack of separate air and irrigation channels and limited scope tip deflection [8, 9].

The clear advantage of video endoscope was the image quality, which was of high-definition (HD) quality, and provision to use narrow-band imaging (NBI) technology to delineate tumour tissue [9]. However, this advantage was offset by previously mentioned shortcomings. Many of these limitations were addressed by the next-generation single-operator cholangioscope.

Fig. 2.1 Two operator video–cholangioscope 'Mother–Baby' endoscopes

2.4 Single-Operator Cholangioscopy: Catheter-Based System

Catheter-based systems are in principle based on mother–baby scope concept. A commercial catheter-based cholangioscope—SpyGlass Direct Visualization System or now known as the 'legacy' system (Boston Scientific, MA, USA)—was introduced in 2007 as a first single-operator cholangioscopy platform (Fig. 2.2). This system successfully addressed the limitation of traditional video endoscopes [9–11]. The cholangioscope (spy scope) was a 10-Fr-diameter catheter with four lumens. A 0.9-mm channel, which allowed the passage of a reusable optical probe (spy probe), two separate 0.6-mm irrigation channels and a 1.2-mm working channel to allow a slim biopsy forceps for visually targeted biopsies (spy-bite) or a laser/electrohydraulic (EHL) lithotripsy probe for therapeutic applications. The scope had four-way tip deflection allowing 70-degree view in up–down deflection and a limited 30-degree view on right–left deflection. The probe was connected to a proprietary light source and a colour image sensor camera. The scope is inserted through the accessory channel of a standard duodenoscope, usually over a guidewire, into the biliary tree. This system had multiple advantages such as single-operator function; separate channels for irrigation; four-way tip deflection; and improved manoeuvrability and was partially disposable [7, 11, 12]. Owing to its advantages, the system did become popular in clinical practice with a large amount of published literature on its utility and potential uses [7, 10–12]. The system was not without its limitations, primarily being the image quality. The image quality was the same and

Fig. 2.2 First generation single operator cholangioscope (SpyGlass, Boston, scientific)

no better than the previous systems, a complete 360-degree view was a challenge, and image quality used to deteriorate after a few uses of the spy probe [7, 9, 11].

Most of these disadvantages were overcome with the launch of a second-generation SpyGlass DS system in 2015, with digital imaging capabilities. The new scope has an integrated CMOS (complementary metal–oxide–semiconductor) image sensor at the tip of scope, obviating the need for a separate spy probe (Figs. 2.3 and 2.4). This produces much-improved digital quality images (Fig. 2.5) with a wide-viewing angle. In addition, the new scope has a tapered tip and better

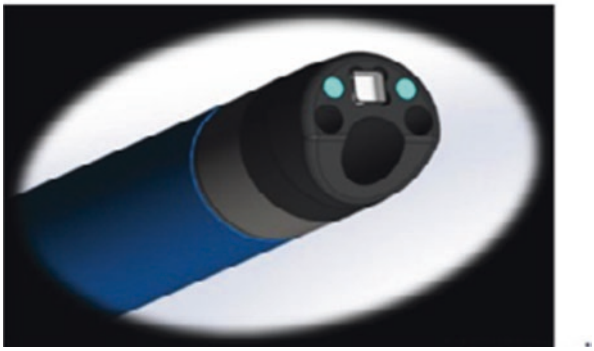

Fig. 2.3 Second Generation digital single operator cholangioscope (SpyGlass DS, Boston Scientific)

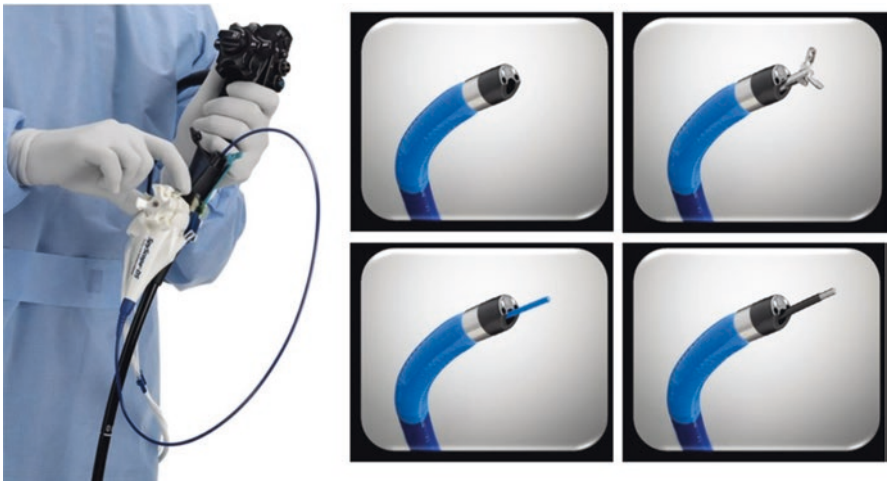

Fig. 2.4 Second generation digital SpyGlass scope with accessories

Fig. 2.5 Comparison of image quality of first generation and Digital spyglass cholangioscopes. (**a**) First generation Spyglass cholangioscopy images. (**b**) Spyglass DS (DIGISPY) cholangioscopy images

ergonomics and is a single-use disposable catheter which ensures that there is no image degradation as was a problem with the 'legacy' system [13].

With better imaging and improved ergonomics, the new single-operator endoscopes are getting popular in clinical practice. However, as this endoscope was introduced recently, the data about its advantages and disadvantages is awaited. There is robust data on application and utility of the first-generation 'legacy' system in literature.

2.5 Direct per-Oral Cholangioscopy

Direct bile duct visualization by a single operator can be achieved by using ultra-slim, forward-viewing endoscopes in patients with dilated bile ducts [14, 15]. These scopes are 5–6 mm in diameter and were originally designed for transnasal or paediatric endoscopies.

The major limitations are difficulty in accessing the bile duct, looping of the scope in the stomach, difficulty to maintain position inside the bile duct and need for presence of a dilated duct.

Usually, the endoscope is advanced over a previously placed guidewire during ERCP. The slim endoscope is then backloaded over the guidewire into the bile duct [15]. A sphincterotomy is usually required for access due to large diameter of the endoscope. Maintaining the guidewire and endoscope position is technically challenging, and a number of techniques including use of inflated intraductal balloons and use of an overtube have been described with good clinical success [16, 17].

2.6 Indications

The major indications and application of cholangioscopy are to manage difficult biliary stones and to establish diagnosis in indeterminate biliary strictures.

There are a host of other indications and therapeutic applications of cholangiopancreaticoscopy in today's endoscopy practice. These include the following.

Major clinical applications:

1. Establish the diagnosis in indeterminate biliary strictures.
2. Intraductal lithotripsy for large or impacted stones.

Other applications:

3. Pancreatic lithotripsy.
4. Evaluation of pancreatic cystic lesions.
5. Staging and extent of intraductal extension of periampullary carcinoma and cholangiocarcinoma.
6. Mirizzi's syndrome.
7. Evaluation of haemobilia.
8. Evaluation of unexplained biliary filling defects.
9. Retrieval of proximally migrated biliary or pancreatic stents.
10. Guidewire placement across difficult strictures.
11. Transpapillary drainage of the gallbladder.
12. Intraductal ablative therapies.
13. Primary sclerosing cholangitis.

2.7 Application and Efficacy

2.7.1 Intraductal Lithotripsy

Cholangioscopy-guided lithotripsy-using electrohydraulic (EHL) or laser lithotripsy (LL) probes in difficult biliary stones, which could not be removed by conventional ERCP, have been well documented in the literature [18–22].

Stone fragmentation under direct vision of a cholangioscope is an exciting application, especially where conventional methods have failed. Both biliary and

pancreatic stones can be targeted by this modality without damaging the ductal wall. Commercial EHL and LL probes are available which can be inserted through the working channel of the cholangioscope and be used for stone fragmentation.

The EHL probe comprises of two coaxial electrodes at the probe tip. Under water immersion, these produce high-energy hydraulic waves that lead to stone fragmentation. Similarly, in laser lithotripsy, a quartz laser fibre produces repetitive laser energy beams, which gets converted to a high-amplitude mechanical shock wave causing stone fragmentation [23].

2.7.2 Bile Duct Stones

Cholangioscopic intraductal lithotripsy using EHL or LL has been documented to be a very successful modality for difficult biliary stones, where conventional methods like mechanical lithotripsy, use of balloon sphincteroplasty followed by basket or balloon extractor have failed. The success rate has been consistently reported to vary between 80% and 100% [11, 18–22]. A multicentre trial with the single-operator cholangioscope system of 297 patients with biliary diseases reported more than 92% success rate with EHL in 66 difficult biliary stones, with complete ductal clearance achieved in over 70% of patients in the first session [22]. Another smaller study of 26 patients, 12 of whom had failed mechanical lithotripsy, showed 100% successful ductal clearance with EHL [21].

Laser lithotripsy (Fig. 2.6) has been shown to be equally effective as compared with EHL. A study from India included 64 patients with difficult biliary stones had 100% success of laser lithotripsy with >83% bile duct clearance in the first session itself [21]. In another multicentre trial, 97% patients were successfully treated with

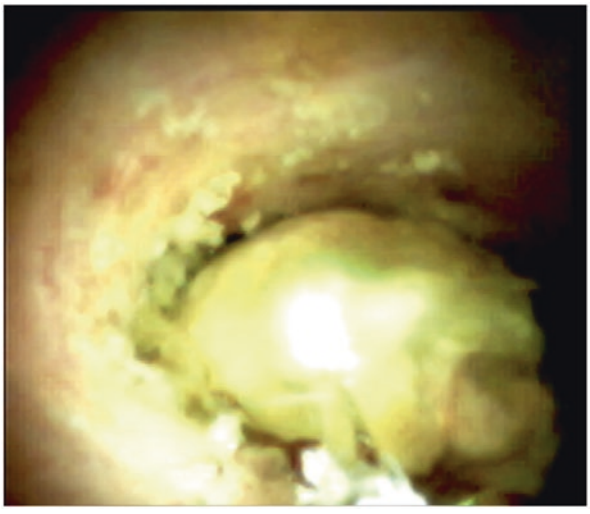

Fig. 2.6. Intraductal laser lithotripsy

Ho–YAG (holmium–yttrium aluminium garnet) laser with >70% success in clearing the bile duct in the first session [24]. Advantages of intraductal lithotripsy are access to difficult areas like cystic duct, intrahepatic stones and stone fragmentation under complete visualization.

Earlier studies have compared extracorporeal shock wave lithotripsy (ESWL) with intraductal lithotripsy with comparable results [25]. ESWL as a primary treatment for biliary stones is no longer a preferred modality as an ERCP is anyway required to remove the stone fragments. Cholangioscopy-guided lithotripsy is a more practical option today. Biliary stones in difficult locations like intrahepatic stones [25] and Mirizzi's syndrome [26] have been shown to be successfully managed with cholangioscopy.

Per-oral pancreaticoscopy (POP) has been used to treat pancreatic ductal calculi, either in conjunction with ESWL or independently. In a few studies, the ductal clearance rates have been reported to be around 70% with pain control in 89% patients [27, 28].

2.7.3 Indeterminate Biliary Strictures

A stricture without an obvious mass on imaging and negative cytology with traditional modalities is considered indeterminate. Conventionally, ERCP with brushings from the stricture, bile cytology and biopsy have been the mainstay for evaluation of indeterminate biliary strictures.

The overall sensitivity of cytology/biopsy vary from <30% to >70% [29–33] with a specificity >90%. The sensitivity rates improve with a combination of different modalities like brushings, aspirate and biopsies.

It is in the definitive diagnosis of these indeterminate strictures that role of cholangioscopy and guided biopsy has been extensively studied and reported.

Multiple characteristics for malignant lesions on cholangioscopic have been described and validated. The presence of dilated, tortuous vessels at the stricture mucosa, described commonly as 'tumour vessels', is an important sign to diagnose malignancy. Other characteristics are presence of intraductal mass or nodules, ulcerated mucosa and presence of papillary and villous mucosal projections (Figs. 2.7, and 2.8) [34, 35]. Visualization alone, in a series of video cholangioscopy, was enough to make a diagnosis of malignancy in 92% of patients [36]. Multiple, prospective single-centre studies have shown the cholangioscopic visualization with or without cholangioscopic biopsy has a sensitivity of 90%–100% and a specificity of 80%–95% [37–40] to diagnose biliary malignancies. A large international multicentre trial of a single-operator cholangioscopy system in 297 showed the sensitivity to diagnose malignancy was 66%, and it altered management in 64% patients [21]. In addition, 88% (in 140 patients) cholangioscopic biopsies taken were reported as adequate [21]. In a recent meta-analysis of the catheter-based system, the overall sensitivity and specificity of visualization alone were 90% and 87% for diagnosing

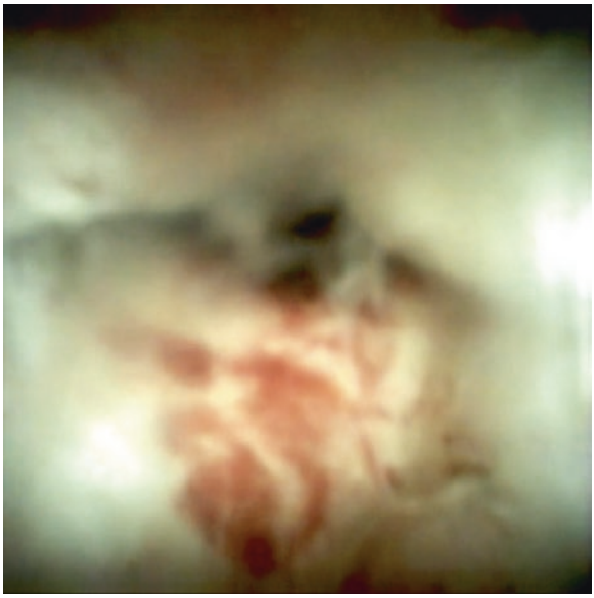

Fig. 2.7. Biliary stricture with neovascularisation and nodular lesion

Fig. 2.8. Biliary stricture–benign

malignancy [41]. When cholangioscopic biopsies were done, the values were 69% and 98%, respectively [41].

At some referral centres, addition of NBI to video cholangioscopy improved visualization of the mucosa and tumour vessels [42].

With the advent of new digital single-operator cholangioscopes, the visualization has improved manifold, and it is expected that the sensitivity rates will further improve. The addition of NBI technology to digital scope will help in accurate malignancy detection.

2.7.4 Primary Sclerosing Cholangitis (PSC)

PSC is another disease with an evolving role of cholangioscopy. In limited series, it has been shown that addition of cholangioscopy to ERCP improves the yield and sensitivity to diagnose malignancy in dominant strictures of PSC [43].

2.7.5 Pancreatic Neoplasms

Per-oral pancreaticoscopy has been used for the diagnosis and to define the extent of intraductal papillary mucinous neoplasms (IPMN) of the pancreas [44, 45]. POP has also been studied in a small series for evaluation and diagnosis of pancreatic strictures [46]. The smaller calibre, tortuosity of pancreatic duct, makes it technically more challenging to directly see the pancreatic duct.

2.8 Other Applications

Few case reports have described the utility of cholangioscopic guided retrieval of biliary and pancreatic stents [47, 48]. Other emerging roles are in the use of ablative therapies and photodynamic therapies for intraductal tumours, which in a few non-randomized studies have been shown to be beneficial [49, 50].

2.9 Complications

Cholangiopancreaticoscopy is generally a safe procedure with complications similar to conventional ERCP. The common complications are due to specific manoeuvres like a wide biliary sphincterotomy, which is required for advancement of the system into the bile duct [6, 7]. Some studies have looked into the complication rates and found that the procedure does carry an added risk over the ERCP, with average complication rates ranging from 3% to 7% [6, 7, 51]. The common complications are cholangitis, which is related to irrigation during the procedure, rarely pancreatitis and bile leaks/haemobilia after lithotripsy [51].

2.10 Recent Data on Efficacy and Safety

Cholangioscopy is quickly establishing itself as a safe and practical option for biliary diseases. A recently published international multicentre trial for efficacy and safety of EHL and laser lithotripsy concluded that both cholangioscopic modalities were equally effective in more than 95% patients with an excellent safety profile [52].

Recent data from a multicentre international registry for cholangioscopy in indeterminate biliary strictures in more than 250 patients showed that cholangioscopy altered patient management in approximately 85% patients [53].

Preliminary data from our own centre showed that cholangioscopy affected the diagnosis in indeterminate biliary stricture in approximately 75% patients and our initial experience with lithotripsy has been encouraging [54].

Recent Indian expert consensus statements [55] emphasize the use of cholangioscopy in indeterminate biliary strictures and difficult biliary stones.

2.11 Conclusion

The rapid technological advances in the past decade have made cholangiopancreaticoscopy a vital diagnostic and therapeutic tool for pancreatic and biliary diseases.

The advent of single-operator system, digital spyglass with excellent images and easier to handle scopes with good therapeutic capabilities has made this modality popular in clinical endoscopic practice.

Future advances will include incorporation of NBI technology within the cholangioscopes, further improvements in imaging quality, less cost and evolution of ablative therapies for intraductal neoplasms.

Recent data on efficacy and safety of cholangioscopy both in difficult stones and indeterminate biliary strictures have been very promising, and have made this a much sought after intervention in biliary diseases.

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Chapter 3
Non-cirrhotic Portal Fibrosis

Vivek Mangla, Shivraj Bahadur Singh, Sujoy Pal, Nabeen Nayak, and Samiran Nundy

3.1 Introduction

In western countries, liver cirrhosis represents the most common cause of portal hypertension (PHT). In India, however, non-cirrhotic causes comprise a major proportion of patients with PHT especially in the younger age groups [1–3]. These are mainly extrahepatic portal venous obstruction (EHO), non-cirrhotic portal fibrosis (NCPF) and hepatic venous outflow tract obstruction (HVOTO). Although NCPF comprised 23 (8%–47%) patients with portal hypertension reported from Indian series in the 1980s [3, 4] its incidence seems to have been decreasing in recent years mirroring the experience in Japan where it was fairly common in the early years of the twentieth century and became rare towards its end [3].

NCPF as a disease entity was first described by Banti in 1889 in a group of patients who had anaemia and splenomegaly without obvious haematological disease [5]. In the late 1950s, the terms *tropical splenomegaly syndrome and Bengal splenomegaly* were used to describe such patients. In the early 1960s, a distinct group of patients were identified in Calcutta (present-day Kolkata), Delhi and Chandigarh who presented with recurrent episodes of massive upper gastrointestinal (GI) bleeding without ascites or encephalopathy who had normal, smooth surfaced livers. The term non-cirrhotic portal fibrosis (NCPF) was first used for them by Basu et al. (1967) and endorsed by the Indian Council of Medical Research (ICMR) in

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1969 [6]. A similar condition, albeit with subtle differences, was also reported from Japan, and was called *idiopathic portal hypertension* (IPH). Recently, the term 'non-cirrhotic portal hypertension' has been proposed to describe these patients.

3.2 Definition

In 2007 the Asia Pacific Association for the Study of the Liver (APASL) working party on portal hypertension defined NCPF as 'a disease of uncertain aetiology characterized by periportal fibrosis and involvement of small and medium branches of the portal vein, resulting in the development of portal hypertension with primarily normal liver structure and function' [3].

3.3 Epidemiology

Although this disease entity has been reported worldwide, the highest incidence has been reported from developing countries especially among the lower socio-economic groups. In India, its incidence ranges from 7.9% to 46.7% in reported series of patients with portal hypertension [3]. As mentioned earlier worldwide, including in India, the incidence of NCPF seems to be decreasing in recent years possibly due to improvements in hygiene and living conditions [3]. However, recently, two series of children have described idiopathic portal hypertension with features being quite similar to NCPF [7–9]. In children, NCPF has been reported to comprise 3.3%–4.6% of all patients with portal hypertension [7, 9]. Idiopathic portal hypertension is also being increasingly recognized in patients with HIV infection [10, 11].

3.4 Aetiopathogenesis

There is no identifiable single agent implicated in the aetiopathogenesis of NCPF. The following hypotheses have, however, been proposed:

1. *Infections*
   Abdominal infection at birth or in early childhood including umbilical sepsis, bacterial infections or diarrhoeal episodes leading to portal pyaemia and pylephlebitis may result in thrombosis, sclerosis and therefore obstruction of the small- and medium-sized portal vein radicals. However, whether the primary event is sclerosis or thrombosis is not clear. In experimental studies, similar changes have been reported after injection of dead non-pathogenic bacteria (*E. coli*) into the portal veins of rabbits and dogs [12].
2. *Exposure to chemicals, trace metals and certain drugs*
   (a) Arsenic has often been implicated in the causation of NCPF [13–15]. Liver biopsies from patients living in areas where the groundwater levels of

arsenic are high have shown changes similar to NCPF. Histological examination in these patients reveals periportal fibrosis and incomplete septal cirrhosis, with or without neovascularization within the expanded portal zones. However, in experimental studies, increases in hepatic collagen and hydroxyproline without features of NCPF or portal hypertension have been seen suggesting that arsenic ingestion may not be an important factor in the aetiopathogenesis of this disease.

(b) Using 6-mercaptopurine, azathioprine and corticosteroids has also been implicated as a causative factor in some studies [13–15]. However, no report has consistently or conclusively been able to prove the impact of these drugs in aetiopathogenesis of NCPF.

(c) Other factors.

These include pica, chronic exposure to vinyl chloride monomers and copper sulphate (in vineyard sprays) and protracted treatment with methotrexate and vitamin A.

3. *Altered Immunity*

Patients with NCPF have reduced cell-mediated immunity. There is a decrease in T8 cells, an alteration in the T4/T8 cell ratio and increased VCAM-1 and soluble TNF receptors I and II. The role of these changes in the pathogenesis or whether they are the result of the disease process is still unclear. IPH, as reported from Japan, is associated with autoimmune disorders such as systemic lupus erythematosus, progressive systemic sclerosis, thyroiditis and mixed connective tissue disease with elevated anti-ds DNA and anti-nuclear antibodies.

4. *Genetic predisposition*

Familial aggregation and a high frequency of HLA-DR3 have been reported.

5. *Unifying Hypothesis*

Investigators in India have proposed that in genetically predisposed individuals, NCPF develops possibly following a thrombotic event occurring in the extrahepatic portal venous system soon after birth or early in life causing obstruction to these veins and dislodging thromboemboli into the portal vein branches. Subsequent incorporation of the emboli into the walls of some of these medium- and large-sized intrahepatic veins and their organization and sclerosis renders the vascular walls irregularly thick and rigid. Veins in the small portal tracts further ahead become obliterated and replaced by multiple fine channels. These changes result in resistance to portal blood flow and portal hypertension manifesting around a young adult age [16–19].

3.5 Pathology

The appearance of the liver in NCPF varies widely, ranging from near normal with only a mild increase in firmness and a ‘beefy’ look on its cut surface to areas of nodularity (about 10%–15% cases) and/or atrophy with moderate firmness [18, 20]. The diffuse nodularity with diffuse fibrosis throughout the entire organ that is seen in cirrhosis is never present. The variable appearance is also reported in explant

livers from long-standing cases of NCPF presenting as end-stage chronic liver disease diagnosed as cryptogenic cirrhosis [18].

Histological features of NCPF are chiefly three, namely, portal fibrosis of varying grades and extent, an absence of cirrhosis and alterations in randomly distributed portal vein branches. The first two are non-specific but strongly suggestive of NCPF in the clinical setting, while the last, which is characteristic of the disease, is encountered only in rare deep wedge biopsies and inadequately sampled explant and autopsy livers [18, 20]. Portal fibrosis and an absence of cirrhosis justify the term NCPF reported worldwide under various other names [18]. Portal tract fibrosis is of variable degree and spatial distribution, some parts of the liver having minimal or no fibrosis such that an aspiration biopsy may show normal hepatic parenchyma (Fig. 3.1a, b & c) [18, 20, 21]. Portal fibrosis often links up neighbouring portal tracts and sometimes partly or completely outlines a roughly nodular area of hepatocytes with the efferent hepatic vein tributary (centrilobular vein) in the centre (Fig. 3.1a & b). Histological confirmation of the absence of cirrhosis is important in

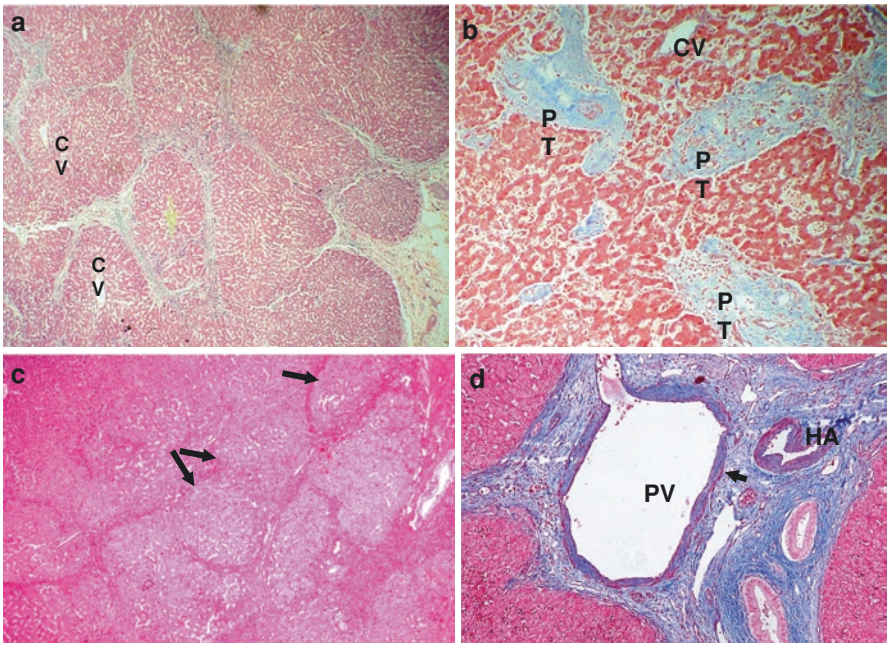

Fig. 3.1. Spectrum of histological abnormalities in livers of NCPF. (**a**) Portal tracts frequently show increased fibrous tissue and link up with adjacent ones partly isolating parenchymal nodules around efferent hepatic vein tributaries in the centre (CV). (**b**) Normally prominent portal vein branches in the fibrosed small portal tracts (PT) have been replaced by small inconspicuous vessels. (**c**) Small nodular groups of regenerating hepatocytes (arrows) are separated by thin plates of atrophic parenchyma, a picture different from cirrhosis (see Fig.3.2, left). (**d**) Irregular sclerotic thickening of a medium size portal vein (PV) wall with original thin muscular wall at the periphery (arrow), a feature characteristic of NCPF. Compare with accompanying normal appearing hepatic artery branch (HA)

management and prognosis. In aspiration biopsy and whole liver specimens, even with significant portal fibrosis, the diffuse nodularity and diffuse fibrosis of cirrhosis are lacking (Figs. 3.1a, b & c and 3.2 left half), and in deep wedge biopsies while the subcapsular area may resemble cirrhosis, the deeper area is distinctly non-cirrhotic (Fig. 3.2 right half a & b). Nodular hyperplasia of the hepatocytes is relatively rare and focal in distribution. Regenerative nodules are characteristically absent, thus differentiating NCPF from cirrhosis. It is also different from the nodular transformation of cirrhosis in that the nodules are inconspicuous and are separated from one another not by fibrous septa but by atrophied hepatocytes (Fig. 3.1c). Inflammation is minimal to mild in the portal tracts and none in the lobular parenchyma.

Histological abnormalities unique to NCPF that involve randomly distributed large- and medium-sized portal vein branches manifest as irregular fibrous thickening of the vessel walls compromising the luminal space, while the original thin muscle wall of the vein can be seen on the outside (Fig. 3.1d). Organized mural thrombi are sometimes present on the luminal side [18, 20]. Because of the location of such vessels, these NCPF-specific changes are encountered in some deep wedge biopsies, and in sufficiently sampled whole livers but almost never in aspiration biopsies. In some of the fibrosed smaller portal tracts, the normal portal vein branch is replaced by several small vessels (Fig. 3.1b), possibly representing new vessel

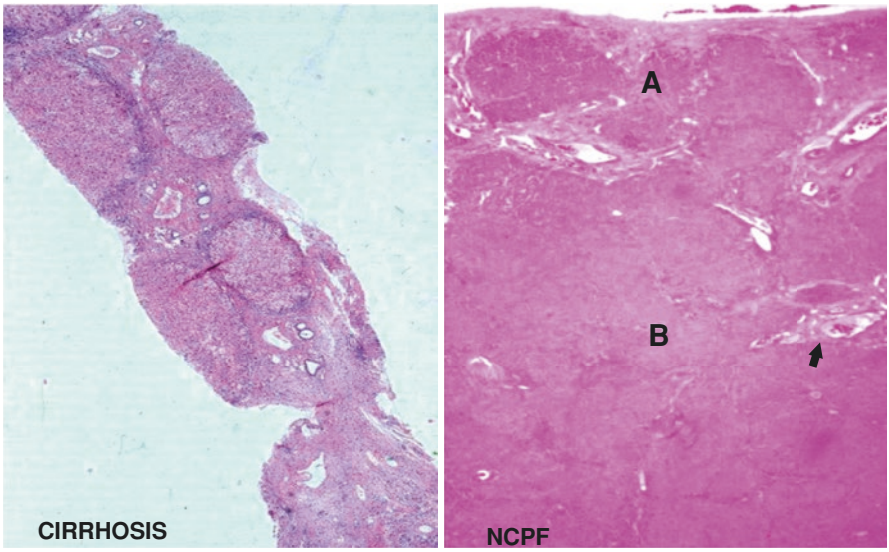

Fig. 3.2. *Right* Deep wedge biopsy of liver in a case of NCPF. The subcapsular area (**A**) shows irregular small nodules with some fibrous septa in between resembling cirrhosis. The deeper parenchyma (**B**) on the other hand appears normal except for mild fibrosis in some portal tracts (arrow). The total picture is thus not of cirrhosis (compare with picture on left). *Left* Aspiration liver biopsy shows parenchymal nodules separated by fibrous septa throughout the deeper parenchyma, a picture characteristic of cirrhosis

formation subsequent to occlusion of the original vein branch. All these changes have prompted the use of the term ‘occlusive portal venopathy’ [20]. A staging system based on pathological and imaging features has been suggested for idiopathic portal hypertension (IPH), a disease equivalent to NCPF in Japan [22]. This staging system in IPH is based on gross and imaging features. Stage 1 is characterized by a non-atrophic liver without subcapsular parenchymal atrophy, stage II by a non-atrophic liver with subcapsular parenchymal atrophy, stage III by an atrophic liver with subcapsular parenchymal atrophy and stage IV by portal venous occlusive thrombosis [22].

3.5.1 Ultrastructure

There is widening of the space of Disse. Haphazardly arranged collagen bands in the perisinusoidal space are also seen [23]. Hepatocytes show only a mild change manifested by an increase in lysosomes and fat droplets without changes in the mitochondria or endoplasmic reticulum [20].

3.6 Haemodynamics

There is a marked elevation in the portal venous pressure, with pressure gradients noted between the spleen and liver and between the intrahepatic and wedged hepatic vein measurements [24] suggesting two possible sites of obstruction, pre-sinusoidal and sinusoidal. However, in most patients the site is pre-sinusoidal with only a small proportion of patients having evidence of perisinusoidal obstruction [3, 25]. In these patients the hepatic venous pressure gradient is normal or near normal, and there is a marked increase in splenic and portal vein blood flow.

3.7 Clinical Features

NCPF is a disease which mainly affects young and middle-aged patients. The duration of symptoms at presentation varies from 15 days to 18 years. Most patients present with a history of upper GI bleeding without hepatic decompensation. There is usually a massive enlargement of the spleen which causes recurrent left upper quadrant abdominal pain because of perisplenitis and splenic infarction. Features of hypersplenism are present in nearly half the patients. The liver may appear normal or enlarged with some scattered nodules, but the peripheral stigmata of chronic liver disease are usually absent. Jaundice and hepatic encephalopathy are extremely rare. In a recent series of 30 patients from India, 87% had hypersplenism, 30% presented with upper GI bleeding and 60% had anaemia with splenomegaly [26]. Recent data

from the West reported that a sizeable proportion (20%–58%) of IPH patients may be asymptomatic [27]. Rarely patients may present with glomerulonephritis or hypoxaemia due to pulmonary arteriovenous fistulae. [28]_ENREF_87 The disease is generally considered to be more common in men compared to women though there is no unanimity on this data.

3.8 Laboratory Features

Haematology: Anaemia is common and is usually microcytic and hypochromic in type due to blood loss from multiple episodes of variceal bleeding as well as hypersplenism (which is also accompanied by leukopenia and thrombocytopenia). There may occasionally be coagulation and platelet function anomalies with mild compensated disseminated intravascular coagulation (DIC) secondary to endotoxaemia [29]. The activity of ADAMTS13 (disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), a zinc-containing metalloprotease which cleaves von Willebrand factor, is reduced in these patients [30].

Liver function tests: The routine liver function tests are usually normal. However, deterioration in liver function has been reported in some patients with histopathological findings revealing NCPF. This has been described in about 1% patients undergoing liver transplantation in a series from India with MELD scores ranging from 9 to 22 [31].

Viral serology: Because the majority of patients with NCPF present with variceal bleeding and are likely to have received blood transfusions, viral serological examination should be done to rule out co-existing hepatitis B or hepatitis C.

Vitamin B 12 levels: Recently, it has been reported that vitamin B12 levels are lower in patients with idiopathic non-cirrhotic intrahepatic portal hypertension compared to patients with cirrhosis [32].

3.9 Imaging

Ultrasonography with Doppler (Fig. 3.3) is the investigation of first choice. The spleen is enlarged; the splenoportal venous axis is dilated and patent with dilatation of the portal vein and its main branches. There is a sudden narrowing or cut-off of the intrahepatic second- and third-degree portal vein branches resulting in a 'withered tree' appearance together with approximation of the vascular channels [33]. Spontaneous lienorenal shunts may be present in 10%–15% of patients. The presence of delayed periportal enhancement on contrast-enhanced ultrasonography (CEUS) using the perflubutane microbubble technique may be helpful in differentiating IPH from cryptogenic cirrhosis. In cirrhosis, a homogeneous enhancement of the parenchyma has been observed [34].

Fig. 3.3. B-mode color Doppler USG images showing dilated portal and splenic veins, with hepatopetal flow. Courtesy: Dr Madhusudhan KS, Department of Radiodiagnosis, AIIMS, New Delhi, India

Acoustic radiation force impulse (ARFI) elastography may be helpful in differentiating IPH from cirrhosis and chronic hepatitis with a higher ratio of spleen/liver stiffness >1.71 being observed in patients with IPH [35].

CT angiography may help differentiate NCPF from cirrhosis. It shows a patent and dilated portal vein, gross splenomegaly with usually no ascites and a normal liver morphology (Fig. 3.4).

Earlier *splenoportovenography* was the investigation of choice before Doppler and CT became available. It is now essentially of only historical interest. It reveals a markedly dilated portal and splenic veins with a 'prune tree' appearance of the intrahepatic portal vein branches. There are frequent and extensive collaterals, and natural shunts have been reported in about 16% patients with NCPF [33].

3.10 Endoscopy

Oesophageal varices are present in 85%–95% of patients with NCPF. These varices are generally larger (90%) than those in cirrhotic patients (70%). Gastric and anorectal varices are seen more commonly in NCPF than cirrhosis. Portal hypertensive gastropathy is uncommon and usually develops after variceal obliteration.

3.11 Hepatic Venous Pressure Gradient

The hepatic venous pressure gradient is usually normal as the obstruction is generally pre-sinusoidal. However, it may be elevated in a small proportion of patients with NCPF as has been reported in a study from India [26]. This test is of particular value in patients where liver cirrhosis cannot be ruled out on clinical grounds and a liver biopsy (taken through the transjugular route) is required to establish the diagnosis. It is also a useful test in patients with hypersplenism when a percutaneous liver biopsy would be risky due to the presence of thrombocytopenia.

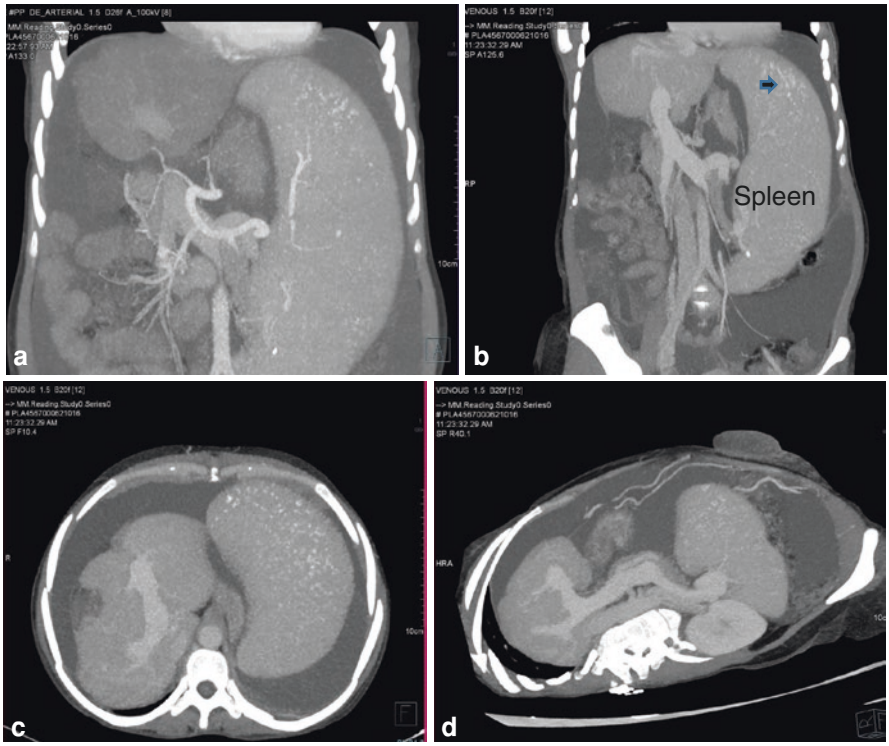

Fig. 3.4. Coronal arterial phase CT image showing splenomegaly with enlarged splenic artery (**a**); Coronal venous phase CT image showing dilated splenoportal axis, splenomegaly, Gamna-Gandy bodies (solid arrow) and ascites (**b**) Axial and oblique axial CT images showing dilated splenoportal axis with abrupt change in calibre of the intrahepatic portal vein (**c** & **d**). Courtesy: Dr Madhusudhan KS, Department of Radiodiagnosis, AIIMS, New Delhi, India

3.12 Liver Biopsy

A liver biopsy may be helpful to establish the diagnosis of NCPF and exclude cirrhosis and other causes of PHT. At surgery, a deep-core wedge along with a needle biopsy has been recommended [3]. However, a Trucut biopsy may suffice in patients who are being managed medically. This may be obtained via the percutaneous or the transjugular route with the latter being preferable in patients with thrombocytopenia. Hillaire et al. have considered four pathological characteristics to diagnose NCPF/IPH; these are hepatoportal sclerosis, periportal fibrosis, perisinusoidal fibrosis and nodular regenerative hyperplasia [36]. The liver biopsy specimen must be longer than 1 cm with >5 complete portal tracts (CPTs) along with alternation of CPT and central veins to exclude cirrhosis; and more than 2/3 (66%) of CPTs should have an absence or reduced calibre portal venules with sclerosis or thickening of their smooth muscle walls [37].

3.13 HIV and NCPF

NCPF in the setting of HIV and AIDS needs special mention. The prevalence of NCPF in HIV is around 0.45%–1% and is rapidly increasing. This has been attributed to recurrent opportunistic gut infections, the use of highly active antiretroviral therapy (HAART) especially didanosine, hypercoagulability and a direct effect of the virus. However, the exact mechanism still remains unclear. HIV-related NCPF occurs predominantly in males and homosexuals and is associated with a prolonged duration of infection. Liver decompensation requiring transplantation has also been reported [38].

3.14 Differential Diagnosis

Child's A cirrhosis: Patients with Child's A cirrhosis have normal liver function tests. However, a very large spleen with a dilated and thickened portal vein on ultrasonography favours NCPF. Viral serology and finally histology usually differentiate NCPF from Child's A cirrhosis.

EHO: Patients with EHO tend to present a decade earlier than those with NCPF. The spleen also tends to be slightly smaller in patients with EHO. An ultrasound Doppler or a CT angiography clinches the diagnosis with a patent thick-walled portal vein being suggestive of NCPF, whereas EHO would be characterized by the presence of a portal cavernoma.

Tropical splenomegaly syndrome: In this condition portal hypertension is uncommon. Additionally, these patients have elevated serum IgM levels and high malarial antibody titres.

IPH: Patients with IPH tend to be older in age and more likely to be female. There is a lower incidence of upper GI bleeding in this condition with most patients presenting with splenomegaly with or without ascites [39].

3.15 Management

Management is primarily focused on dealing with an acute episode of variceal bleeding followed by secondary prophylaxis against its recurrence.

Primary prophylaxis: Exsanguinating haemorrhage is the most common cause of death in these patients. Therefore, in patients with large varices, endoscopic ligation may be considered although there is little evidence supporting the prophylactic use of endoscopic interventions in patients with NCPF. There is no consensus on the use of β-blockers. One small study from India did, however, find β-blockers and

endoscopic variceal ligation to be equally effective in this setting [40]. A recent study on 45 children with NCPF (who had/had not yet experienced an episode of variceal bleeding) has reported good outcomes with prophylactic endotherapy in patients in high-grade varices [9]. Balloon-occluded retrograde transvenous obliteration (BORTO) is another prophylactic option which may be considered in patients with large gastric varices.

Shunt surgery has a limited role in primary prophylaxis. A study from India revealed that although prophylactic surgery was safe, it was associated with a 53% morbidity (hepatic encephalopathy, glomerulonephritis, pulmonary arteriovenous fistula and ascites) on long-term follow-up and consequently prophylactic surgery is not recommended [41]. These findings concur with the recommendations of the APASL working party [3].

3.15.1 Acute Variceal Bleeding

These patients should be managed with endoscopic treatment after initial resuscitation and institution of medical therapy with somatostatin or terlipressin infusion [42]. Variceal band ligation and endoscopic sclerotherapy have been found to be equally efficacious (95% success). A combination of pharmacotherapy and endotherapy can have an additive effect [43]. Surgery to control variceal bleeding is required in less than 5% of patients and is reserved for patients in whom medical and endoscopic therapy has failed, i.e. who have continued variceal bleeding after two endoscopic treatments during a single admission. In the emergency setting also, if feasible, shunt surgery is preferable over devascularization. Additionally, early direct ligation of the bleeding varix helps control bleeding and stabilize the patient during the initial part of surgery.

3.15.2 Prevention of re-Bleeding

Non-surgical treatment: β-Blockers and endotherapy have been used extensively for prevention of re-bleeding. Endoscopic variceal ligation is considered to be superior to drugs alone for bleeding oesophageal varices. Cyanoacrylate glue injection and the recently introduced endosonography (EUS)-guided coil embolization are generally recommended for gastric varices. β-Blockers have been used in patients with ectopic and difficult-to-treat varices and those who have recurrent varices even after endotherapy or surgical devascularization. Recently, transjugular intrahepatic shunts (TIPS) have also been used in patients with NCPF [44]. The results from various endoscopic series of NCPF are described in Table 3.1.

Table 3.1 Endoscopic series for NCPF

Author (year)	n	Variceal obliteration rate (%)	Sessions required	Follow-up (months)	Complications (%)	Variceal recurrence (%)	Re-bleeding (%)	Bleed-related deaths	Survival (%)	Remark
Sarin 1986 [45]	31	–	1.6 ± 0.9	17.5 ± 5.7	22.5	22.5	3.3	0	100	Only patients achieving variceal eradication included No late deaths
Bhargava 1989 [46]	60	88	8.43 ± 4.82	28.1 (3 months–5 years)	12	15	28	4	86 *at 5 years*	85% follow-up Interval bleeding: 21 episodes Poorer survival in patients with poor liver functions
Bhargava 1991 [4]	83	87	7.33 ± 2.1	37	10	16	23 (prior to eradication)	6	73.6 *at 7 years*	–
Chawla 1997 [47]	72	90.3	5.7 ± 3.0	21.4 +/– 20.4 (1–96)	25	13.9	9.2	2	–	Interval bleeding 17.3%
Dhiman 2002 [33]	45	–	6 ± 3.2		25	14		1	–	21 patients lost to follow-up
Prasad 2019 [9]	45		5 (2–12)	6–42		36%	22%	3	–	Shunt/devasc: 4 patients Liver transplantation: 4 patients

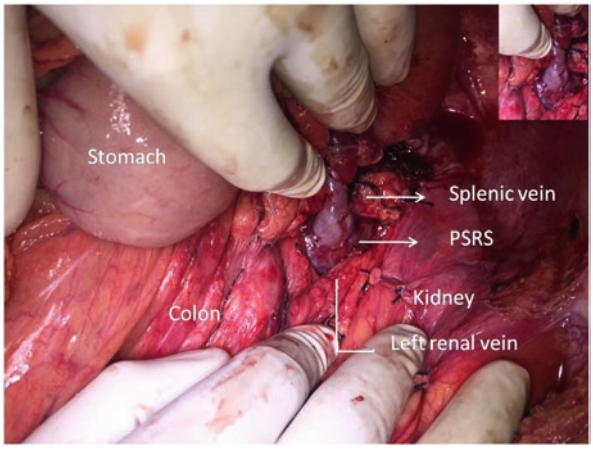

Fig. 3.5. Operative photograph showing a proximal splenorenal shunt (Linton's shunt)

Surgery: Surgery in the form of a splenectomy and lienorenal shunt (Fig. 3.5) is a good option for patients with frequent re-bleeding refractory to endotherapy [48]. It also carries the added advantage of simultaneously treating symptomatic hypersplenism. It is also a good one-time option for patients from remote areas for whom access to healthcare facilities in general and endoscopy in particular is limited. The re-bleeding rates are lower with surgery with less risk of ectopic varices or portal hypertensive gastropathy.

Surgical options include portosystemic shunts and devascularization [33, 41]. We prefer a proximal lienorenal shunt for prevention of variceal re-bleeding. Unlike EHO there is an association of shunt surgery with encephalopathy (about 13%) both clinical and subclinical, nephropathy and myelopathy in NCPF. In view of the risk of encephalopathy, devascularization procedures have been described, the results of which are described in Table 3.2.

Generally, encephalopathy can be managed with medical measures and only rarely does this cause severe debilitation. In our experience, three patients with severely debilitating encephalopathy required shunt embolization or ligation. Some patients with NCPF develop severe impairment in liver function over time [51, 52]. In a recent series from India of 402 transplant patients, 5% had NCPF on final histology [31]. Fifty per cent of these patients had encephalopathy, and 50% had a history of spontaneous bacterial peritonitis. The MELD scores of patients in this series ranged from 9 to 22. This data suggests that a small subset of patients with NCPF can have such impairment of liver function so as to require a liver transplant [51].

Endoscopic therapy and portosystemic shunt surgery are both safe and effective in patients with NCPF for secondary prophylaxis [3]. There is insufficient data on the role of TIPS in these patients, and we propose the following algorithm for the management of NCPF patients (Fig. 3.6).

Table 3.2 Surgical series for NCPF

Author (year)	n	Procedure	Operative mortality (%)	Follow-up (months)	Variceal re-bleeding (%)	Remark
Sama 1971 [49]	16	Splenorenal shunt	6.25	6–48	18.8	
	9	Portocaval shunt	22.2	12–120	–	
	3	Splenectomy with transgastric resection of gastric varices	0	–	33.3	One bleed related death in follow-up
Mathur 1999 [50]	22	Modified Sugiura's	4.5	53 ± 34	0	Three late deaths (none bleed related) 5-year survival: 82%
Pal 2002 [48]	285	PSRS	0.8	–	8	Elective surgery Encephalopathy: 13% 15-year cumulative survival: 88%
Dhiman 2002 [33]	53	Shunt 46, devascularization 7	8	–	–	Encephalopathy: 2%
Pal 2005 [41]	45	PSRS 41, splenectomy alone: 2, splenectomy with devasc: 2	0	49 (12–236)	2.6	Surgery as primary prophylaxis 7 patients lost to follow-up No bleed-related deaths 2 deaths on long-term follow-up; 1 unrelated, 1 due to chronic renal failure 47% long-term morbidity (encephalopathy, glomerulonephritis, hypoxaemia, ascites requiring diuretics)
Prasad 2019 [9]	4	PSRS: 3 Devasc: 1	0	–	–	No mortality/morbidity

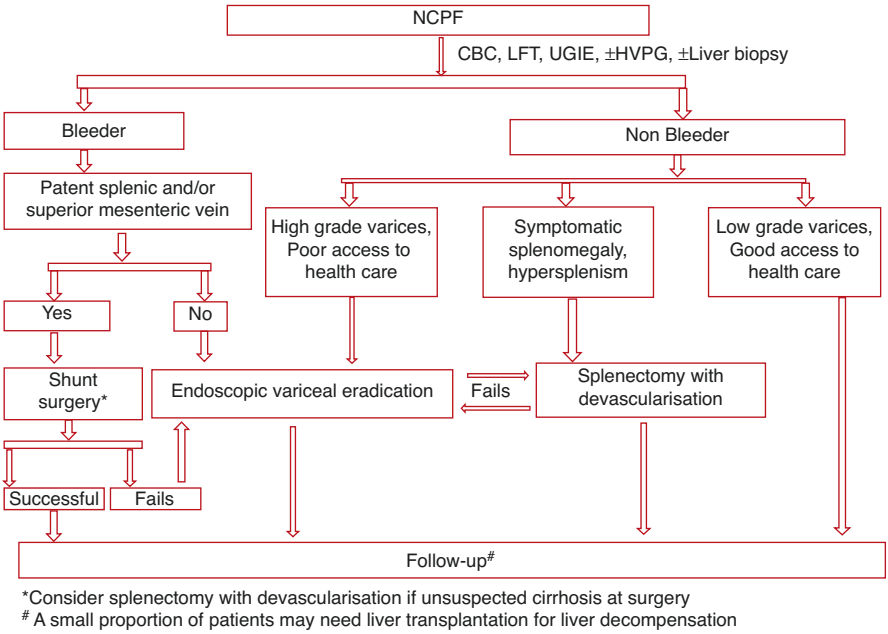

Fig. 3.6. Algorithm for management of patients with NCPF

3.16 Limitations of Data Available on NCPF

There is little information on the natural course of NCPF. There are no randomized trials available comparing endotherapy with surgery for prevention of re-bleeding. There is also a lack of information regarding whether the complications seen in patients occur in the natural course of disease without intervention or are related to the interventions done for their management.

3.17 Summary

NCPF is a disease characterized by moderate to massive splenomegaly, evidence of portal hypertension, with or without hypersplenism, a patent splenoportal axis and hepatic venous outflow, normal or near-normal liver function tests, normal or near-normal hepatic venous pressure gradient and no evidence of parenchymal injury or cirrhosis. Its aetiology still remains unknown. Most patients present with massive variceal bleeding which remains the most common cause of death. Patients who have had major upper GI bleeding may be managed with a proximal lienorenal shunt, while those who have not bled should not be offered surgery. Primary prophylaxis with endotherapy may be considered in patients with high-grade varices. Treatment outcomes are generally good, though some patients may develop portal vein thrombosis, worsening of liver function and ascites over time.

Editorial Comments

Non-cirrhotic portal fibrosis (NCPF) is a global disease but commonly seen in developing countries including India. Its aetiology remains largely elusive, though infection, toxins, immunological disorders, genetic predisposition, etc. had been suggested but not conclusively proven.[1] Irrespective of the aetiology, fibrosis in the small- and medium-sized, intrahepatic portal venous branches is seen in NCPF, the so-called obliterative portal venopathy. The periportal fibrosis seen in NCPF is believed to be related to recurrent episodes of microembolism of the portal venous branches resulting from intraperitoneal sepsis causing portal pyaemia.[1] Sato et al.[2] suggested endothelial–mesenchymal transition phenomenon as the cause of periportal fibrosis. They believed endothelial cells of the portal vein branches have the ability to express mesenchymal cells leading to fibrosis. In fact they have shown that transforming growth factor beta can induce this. Once transformed, type 1 collagen is synthesized from these cells to produce obliterative venopathy which in turn causes portal hypertension. The role of nitric oxide synthetase, both inducible and endothelial (I NOS and E NOS), has also been highlighted by Schouthen et al.[3] With the expression of these in splenic sinus endothelial cells, splenic sinus dilatation occurs causing splenomegaly with a resultant increased splenic blood flow and portal vein pressure.

The liver, macroscopically, usually looks normal, enlarged or shrunken at times. Its surface is usually smooth but can be irregular. The capsule is usually thickened. On histology, the portal vein is characteristically dilated with thickening of the medium and small branches. These veins may have thrombi too,[4] with resultant obliteration of these channels. Simultaneously, there are an increased number of portal venous channels, often termed angiomatosis. The dilated portal veins at times can be seen herniating into the parenchyma representing paraportal collaterals. The sinusoids are usually dilated (so-called mega sinusoids).[5–7] In spite of these abnormalities, the liver architecture is usually maintained. However, there can be atrophy of the liver secondary to deprivation of portal flow in the affected area. The better-perfused area may undergo hyperplasia. The natural history of NCPF is not exactly known.

For reasons mentioned earlier, the liver in NCPF may slowly become atrophic due to reduced portal supply at the periphery (so-called parenchymal extinction). This is particularly so in patients where compensatory arterial hypertrophy does not occur (further ischaemia). When the degree of ischaemia reaches a critical level, patients may progress to liver failure,[8–11] which occurs in about 5% of all patients with NCPF.[10] Patients with NCPF and end-stage liver disease may require liver transplantation.[10]

NCPF patients have a higher incidence of portal vein thrombosis than cirrhotic patients.[11] In view of this, patients who bleed develop ascites even

though their liver function is normal. For this reason some have suggested anticoagulation therapy.[3]

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Chapter 4
Recent Advances in Benign Anorectal Disorders

Pankaj Garg

Benign Anorectal Disorders
1. Anal Fistula.
2. Hemorrhoids.
3. Anal Fissure.
4. Pilonidal Sinus Disease (PSD).

4.1 Anal Fistula

Anal fistula is an abnormal communication between the anorectum and the skin or a blind tract originating from the anorectum and causing recurrent sepsis [1].

4.1.1 Etiology

Most fistulas are cryptoglandular which develop from suppuration of anal canal glands. About 30–50% of anorectal abscesses develop into fistulas [1]. There are several secondary causes, the prominent of which are tuberculosis, deepened fissures, Crohn's disease, radiation therapy, trauma, non-tubercular mycobacteria (NTM), actinomyces, carcinoma, etc [2].

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4.1.2 Evaluation: Pathology

The pathological testing of tissue (fistula tract) and pus is required for several reasons and can be helpful in identifying associated medical conditions which could change the management of the disease [2, 3].

The associated diseases which can be identified are:

- Tuberculosis (TB).
- Inflammatory bowel disease (IBD) especially Crohn's disease.
- Associated malignancy.
- Rare diseases: non-tubercular mycobacteria (NTM), actinomyces, fungal infections, STDs, etc.

The pathological tests done are mainly to detect tuberculosis and Crohn's disease [2, 3]. In developing countries, TB is the most common secondary cause of anal fistula [2, 3]. Several tests can be done to detect TB like histopathology, AFB (acid-fast bacillus) staining, TB culture, Gene-Xpert, PCR (polymerase chain reaction), etc. Conventionally, histopathology and ZN (Ziehl-Neelsen) carbolfuchsin stains are used. On histopathology examination, the prominent features suggestive of mycobacterial disease were granuloma formation, epithelioid cells, caseation necrosis, and Langerhans giant cells [2, 4]. However, recent studies have demonstrated that the detection rate of histopathology is quite low as compared to RT-PCR (real-time polymerase chain reaction) [4]. In a large study, out of a total of 743 samples (410 patients) tested, 63 samples (57 patients) tested positive for tuberculosis [3]. The sample was positive for tuberculosis in 2/181 (1.1%) in tissue-histopathology, 28/341 (8.2%) in tissue-PCR, and 19/115 (16.5%) in pus-PCR samples [3]. Tissue-PCR had significantly more detection rate than tissue-histopathology to detect tuberculosis (28/341 vs 2/181, $p < 0.00001$) [3]. Among PCR, pus had significantly higher detection rate than tissue to detect tuberculosis (19/115 vs 28/341, $p < 0.0009$) [3].

PCR has quite high sensitivity to detect TB bacilli as it detects both dead and live bacteria [3, 4]. As high sensitivity is associated with chances of false negatives, therefore, a positive PCR test should always be correlated with the clinical picture. A positive PCR along with a background of nonhealing of fistula, development of newer tracts/abscesses, or delayed recurrence (after 3–6 months of the healing of the initial wound) would make a strong case for starting ATT [3].

4.1.3 Evaluation: Radiology

1. *Fistulography*—It was a bit helpful when better investigations like transrectal ultrasound (TRUS) and MRI were not available. It is an economical and convenient choice of investigation but is not very accurate [5]. Therefore, in the present era, there is hardly any indication of fistulography.
2. *CT scan*—Though some centers advocate the role of CT scan in evaluating fistula-in-ano, the role of CT in assessment of fistula-in-ano is limited [6].

CT may be more helpful in identifying perirectal inflammatory disease (rather than fistula) and is good for delineating fluid pockets around the anorectum which require drainage [6]. However, the main disadvantages of CT are the requirement of intravenous and rectal contrast and poor delineation of anal sphincters [7].

3. *Endoanal ultrasonography (EUS)*—EUS is safe, effective, and quite helpful investigation to assess fistula-in-ano [6]. It helps in identifying the location of internal opening and the anatomy and position of fistula tracts including horseshoe tracts and also gives good information about the condition of internal and external anal sphincters [6]. However, EUS is operator dependent, and unlike MRI, the images of EUS cannot be interpreted independently by the operating surgeon. Overall, EUS has been shown to be slightly inferior to MRI to assess fistula-in-ano [8–10]. Apart from being invasive, the main disadvantage of EUS (when compared with MRI) is that the images of the tissues which are farther away from the ultrasound probe are not very clear [11]. However, the accuracy of EUS has been increased with the recently launched three-dimensional software and a post-processing software known as volume rendering mode (VRM) [12]. The long-term results are awaited.
4. *Magnetic resonance imaging (MRI)*—MRI is the best imaging modality available today to detect, delineate, and get details about perianal fistulas [11, 13]. MRI provides precise information about the anatomy of the anal canal, the anal sphincter complex, and supralevator fistulas and the relationship of the fistula to the pelvic floor structures (Fig. 4.1.). It allows accurate definition of the fistula tracts and identification of secondary fistulas and abscesses [14]. MRI has also been shown to alter surgical approach [14, 15] and influence surgical outcome [14, 16, 17]. MRI is identified as the modality of choice for preoperative evaluation of fistula-in-ano [14]. It is recommended to be done in all cases of recurrent anal fistulas [17].

A MRI study done in 229 fistula-in-ano patients found that MRI scan was an extremely useful modality to assess fistula-in-ano [6]. It concluded that MRI had high sensitivity and specificity in detecting fistula tracts and the internal opening. The sensitivity and specificity of MRI in diagnosing fistula tracts were 98.6% and 99.7%, respectively [6]. The sensitivity and specificity in identifying internal opening were 97.7% and 98.6%, respectively [6]. MRI added significant information about complex parameters (additional tract or internal opening, horseshoe tract [18], associated abscess, and any supralevator extension [19]) in about half of the patients [over one-third (34.6%) of simple-looking and in over half (52.5%) of complex-looking fistula-in-ano patients]. The additional fistula parameters detected by MRI (and missed by clinical examination) altered the surgical approach in these patients and also helped to decrease recurrence rate substantially [6]. In anal fistula patients, a significant amount of information is missed on routine history and clinical examination. Therefore, additional preoperative investigation (MRI) should perhaps be done in all simple as well as complex fistula-in-ano patients [6]. Though this study recommended to do MRI in every fistula patient (including

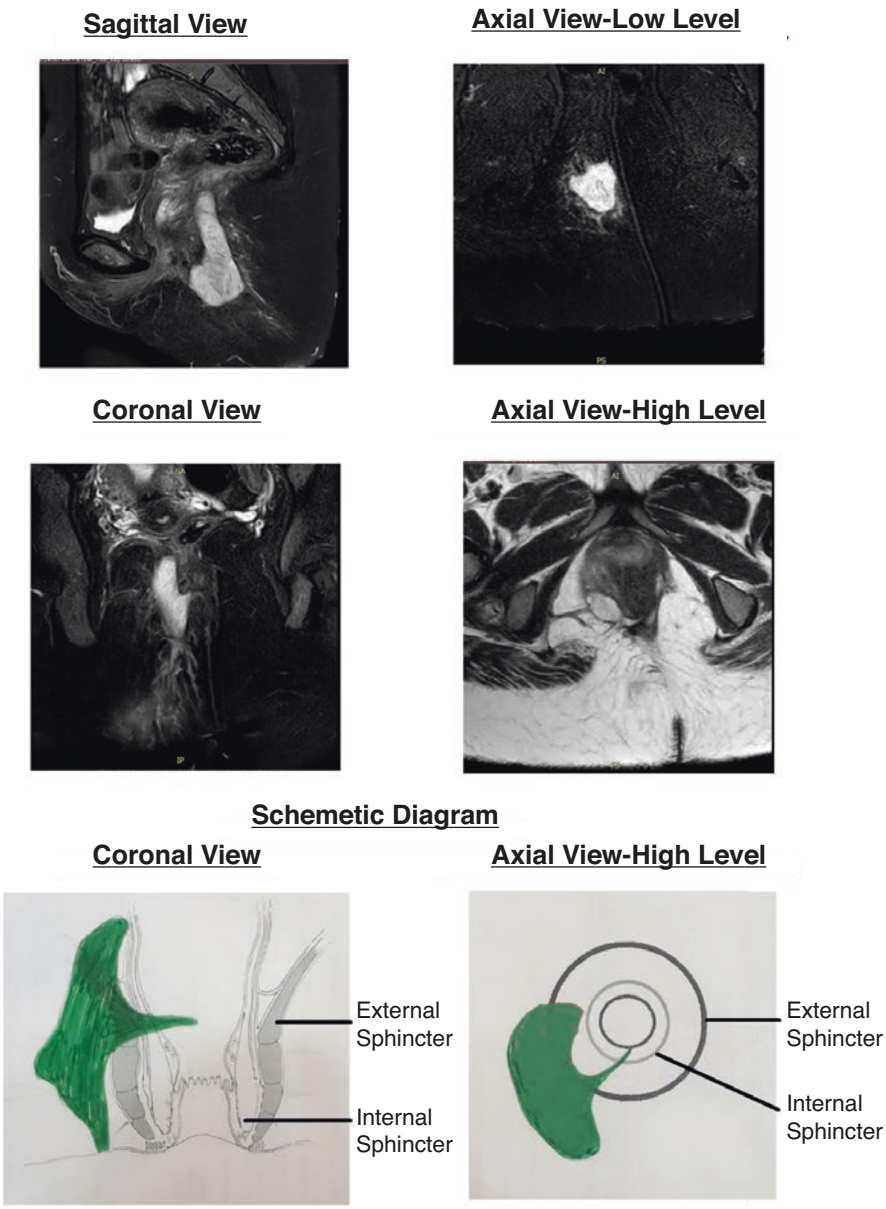

Fig. 4.1. A high transsphincteric fistula with an abscess in a 30-year-old female

simple fistula), this may not seem cost-effective. Therefore, it is prudent to do MRI or EUS in all recurrent and complex-looking fistulas [12].

Recently, MRI has been shown to be of immense value in evaluating fistula healing in the postoperative period [12, 20, 21]. In a study of 1323 MRI scans done in

1003 patients, it was found that MRI was very accurate to identify postoperative complications like abscess, missed tract, and nonhealing of a tract [12]. MRI detected such complications even in apparently clinically healed tracts. Closure/healing of internal opening and intersphincteric tract was assessed accurately by MRI and correlated well with the long-term fistula healing [12, 20]. In a recent study, it was demonstrated that fistulas shown to be healed on MRI between 3 and 6 months postoperatively remained healed on long-term follow-up (median—38 months) in 99.2% (124/125) patients [20]. In early postoperative period (8 weeks), healing (granulation) tissue was difficult to differentiate from active fistula tract/pus [21]. The complete radiological healing took at least 10–12 weeks. So, getting MRI scan for assessment of fistula healing was more accurate after 12 weeks of surgery and therefore should be done after at least 12 weeks [12, 21].

A new scoring system (Garg scores) has also been developed which helps to predict long-term fistula healing on a long-term basis [22, 23]. The Garg scoring is done after 3 months of surgery and is based on six parameters (four on MRI and two clinical parameters). The score can range from 0 to 20. After 3 months postoperatively, score < 8 indicates that the fistula has healed and would remain healed on a long-term basis [22]. On the other hand, a score of ≥8 implies that the fistula has not healed at 3 months and would remain non-healed thereafter. This new scoring was shown to be quite accurate for healing (positive predictive value of 98.2%) [22].

MRI has also led to discovery of a new potential space, "the outersphincteric space" in which the fistula can spread [24, 25]. This outersphincteric space is between the external anal sphincter (EAS) and its covering outer fascia [24, 25]. So, the fistula or abscess in outersphincteric space is lateral to the EAS but does not enter the fat of ischiorectal fossa [24, 25]. The discovery of this space helped to identify a new type of complex fistula—fistula at the roof of ischiorectal fossa inside the levator muscle (RIFIL) [26]. RIFIL fistulas enter the outersphincteric space at low level (mostly at the level of dentate line) and then ascend superiorly in the outersphincteric space in the infero-lateral surface of the EAS and levator (puborectalis) muscle [26]. As these fistulas are in outersphincteric space, they do not enter the ischiorectal fossa and appear juxtaposed to the inferior border of levator muscle [26]. RIFIL fistulas are commonly confused with high infralevator or supralevator fistulas.

4.1.4 Classification of Anal Fistula

Anal fistulas were first classified in 1976 by Parks et al. [27]. After this, another classification was described in 2000 by Morris et al. [28], which is commonly known as "St James University Hospital (SJUH)" classification. This was an attempt to improve the previous Parks' classification which was done in the era when sophisticated radiological modalities were not available. SJUH classification was based on MRI scans and was done by radiologists. In 2005, another classification

was done by Standard Practice Task Force (SPTF) [29]. Recently, Garg has outlined a new classification which is useful for both surgeons and radiologists [30–32].

The purpose of any classification is that it guides regarding:

1. Severity of the disease: The classification should grade the disease in the increasing order of severity. This conveys the level of difficulty in the management of the disease to the treating physician.
2. Management of the disease: The classification should guide the physician regarding the disease management.
3. Prognostication of the disease: The classification should also preferably indicate about the prognosis of the disease.

If the classification is not fulfilling these purposes, then perhaps it is not serving its purpose.

Parks classified all intersphincteric fistulas in one category (grade I) and all transsphincteric fistulas in another category (grade II) [27]. Supralevator and extrasphincteric fistulas were categorized as grade III and grade IV fistulas, respectively [27]. This was the first classification of fistula-in-ano ever done [27]. It was based on clinical findings alone and was done at the time when MRI or endoanal ultrasound was not available (Table 4.1). In this classification, almost all (>92%) of the fistulas were grouped in the first two categories (grades I–II). Moreover, extrasphincteric fistulas were allotted a separate category (grade IV). Recent MRI-based studies in a large number of patients have shown that extrasphincteric fistulas are extremely rare [6, 33], and therefore these fistulas do not warrant a separate category. All transsphincteric were clubbed in one category (grade II) by Parks [27]. Low transsphincteric fistulas (fistulas involving less than one-third of sphincter complex) are quite straightforward (simple) and are conveniently managed by fistulotomy, whereas very high transsphincteric fistulas (fistulas involving more than one-third of sphincter complex) are extremely complex and best managed by sphincter-saving procedures [34, 35]. But Parks classification grouped all transsphincteric fistulas in one category [27]. The same fallacy applies to intersphincteric fistulas which all were clubbed as grade I [27]. Thus, this classification erroneously grouped simple as well as complex fistulas in all the categories (grades I–IV) and obviously had no utility in guiding the operating surgeons with regard to management of the disease [27].

SJUH classification was a slight modification of Parks classification as they bifurcated the Parks grades I–II into four grades (Parks grade I to SJUH grades I and II and Parks' grade II into SJUH III and IV) and combined the Parks grades III (supralevator fistulas) and IV (extrasphincteric fistulas) into one grade (SJUH grade V) [28]. Though this classification was MRI based, it had also no implications on the fistula management as it was practically quite similar to Parks classification.

The Standard Practice Task Force (SPTF) [29] classification was done to guide surgeons to manage the disease (Table 4.1). However, this classification broadly classified all fistulas in just two categories: simple fistulas, in which fistulotomy was safe, and complex fistulas, in which fistulotomy was risky and carried a high

Table 4.1 The fistula-in-ano classifications

Classifications	Parks	St James University Hospital	Standard Task Force	Garg
Grade I	Intersphincteric	Simple intersphincteric	Simple (in which fistulotomy is possible without risk of incontinence) which have fistula involving less than one-third of the sphincter	– *Low* linear (intersphincteric or transsphincteric)
Grade II	Transsphincteric	Complex intersphincteric		– *Low complex* Associated abscess, multiple tracts, or horseshoe tract (intersphincteric or transsphincteric)
Grade III	Supralevator	Simple transsphincteric	Complex (in which fistulotomy has high risk of incontinence). These include high fistula, supralevator fistula, fistula with multiple tracts, horseshoe tracts, anterior fistula in a female and fistula with associated abscess, Crohn's disease, malignancy, and existing continence disturbance	– high linear transsphincteric – fistula with associated comorbidities*
Grade IV	Extrasphincteric	Complex transsphincteric		– *High* transsphincteric with either Associated abscess, multiple tracts, or horseshoe tract
Grade V	Didn't exist	Supralevator		– *High* transsphincteric fistula with Supralevator extension or suprasphincteric fistula or extrasphincteric fistula

LOW fistula, less than 1/3 of external sphincter involvement; *HIGH fistula*, >1/3 sphincter involvement

*Associated comorbidities—Crohn's disease, sphincter injury, postradiation exposure, or anterior fistula in a female

incidence of incontinence (Table 4.1). However, this classification was not based on patient data and hence was not much accurate. Subsequent validation of this classification with patient data demonstrated that one-third of fistulas categorized as complex were actually simple fistulas and could be safely managed by fistulotomy [30]. This classification took too simplistic view of a disease which is so diverse and variable.

As discussed above studies have shown that all the existing classifications (Parks, SJUH, and SPTF) are neither accurate to grade the disease severity nor of much utility from the disease management point of view [30, 36]. So there was a big void due to lack of a good working classification [30, 36]. Garg classification has filled

that void as it provides a lot more relevant information to the operating surgeon (Table 4.1) [30, 36]. Unlike previous classifications, this was the first classification which was validated on the basis of the patient data—clinical findings, MRI, intra-operative findings, and follow-up of 440 patients [30]. This classification has categorized fistulas in five grades (Table 4.1). Garg grades I–II are simple fistulas and can be safely managed by fistulotomy without any risk to continence, whereas Garg grades III–V are complex fistulas, and fistulotomy should not be even attempted in these fistulas [30, 36]. The latter may be dealt with sphincter-saving procedures like anal fistula plug [1], LIFT [37], VAAFT [38], PERFACT [39], and TROPIS [40]. Thus, this classification guides a primary general surgeon regarding the fistulas (grades I–II) which can be easily managed by fistulotomy and the fistulas (grades III–V) in which fistulotomy should not be done and a sphincter-saving procedure may be done. If the general surgeon is not confident or expert in sphincter-saving procedures, then such complex fistulas (grades III–V) may be referred to an expert. Since Garg's is a MRI-based classification, radiologists can use this to report the MRI, and it shall guide the operating surgeons regarding the management of the disease. So, this classification should be used by both radiologists and surgeons. Recent long-term studies have also validated the accuracy of Garg classification in a large cohort of 848 patients with a long-term follow-up [41].

To conclude, Garg classification is a significant advancement over existing classification with regard to accuracy and utility to the operating surgeon [30–32, 36].

4.1.5 Management

4.1.5.1 Medical

There is no role of medical management in treatment of any kind of fistula-in-ano except in Crohn's disease (immunomodulators like infliximab) [42, 43]. Adjuvant medical treatment (antitubercular treatment) is also needed along with surgical treatment in patients of fistula-in-ano with associated tuberculosis [3].

4.1.5.2 Surgical

There is a plethora of procedures developed to treat fistula-in-ano which proves that "*when there are too many treatment options, there is no gold-standard treatment available*."

Broadly, the procedures can be divided into two broad categories.

1. *Sphincter-Cutting Procedures: Mainly for LOW Fistulas.*

Fistulotomy—After passing a probe from external opening and negotiating it through the internal opening, the overlying skin, subcutaneous tissue, internal

sphincter, and small amount of external sphincter are cut open with a knife or electrocautery. The success rate is between 80 and 100% [35, 44]. The incontinence levels are quite low if the patient selection is done properly, and the procedure is done in low fistulas (Garg grades I–II) as identified on clinical examination and MRI [35, 45].

Cutting seton—The seton inserted through the fistula tract is tightened slowly (daily or on a weekly basis) so as to cut gradually through the fresh part of the sphincter while stimulating fibrosis in the older already cut part. The fibrosis would keep the cut part of the sphincter together, thus preventing separation of cut sphincter ends and thereby maintaining continence. The reported success rate is between 80 and 96% but is associated with a high rate of incontinence [46, 47].

2. *Sphincter-Saving Procedures Mainly for HIGH Fistulas.*

Fistulectomy (coring out)—The whole fistula tract is cored out from the skin right up to the internal opening. The defect in the anorectum is closed either primarily with a suture or an advancement flap [48]. This is an adjuvant procedure used with an advancement flap or fistulectomy with primary sphincter repair (FPR).

Loose seton—The seton is not tightened but is kept loose. The main advantage is that it reduces the chances of abscess formation and prevents further spread of fistula. Though the healing rate is quite low, the main advantage is that it doesn't cause any damage to the sphincter complex. This is also used as an adjuvant procedure to decrease infection and initiate "maturity of the fistula tract" before doing a definite procedure [49–51].

Advancement flap—The fistula tract is completely cored out including the internal opening. The defect in the anorectum at the site of internal opening is closed with a flap, which can be either a mucosal advancement flap or anal advancement flap. The reported success rate is between 10 and 75% [52–56] with incontinence rates of 0–52% [50].

Fibrin glue—The fistula is "dried" up by inserting a draining seton for few weeks. Once the fistula tract has dried up, then the internal opening is closed with a suture ligation, and the glue (a tissue adhesive consisting of fibrinogen and thrombin components) is injected into the fistula tract so to promote healing. The reported success rate is between 14 and 69% [57–62] with no risk to incontinence.

Anal fistula plug (AFP)—The fistula tract is curetted and thoroughly washed with saline. A synthetic plug made from porcine intestinal submucosa is inserted in the main fistula tract, and the internal opening is closed over one of the plug ends. The purpose is to promote "biological closure" of the internal opening. The reported success rate is between 14 and 83% [1, 49, 50, 63–65] with minimal risk to incontinence.

Fistula-tract laser closure (FILAC)—In this procedure, the internal opening is closed with a suture ligation. Then, with a ceramic diode laser (12 watts, 1470-nm wavelength), the epithelial layer of the fistula is destroyed with the aim to obliterate the fistula tract without causing any sphincter damage. The reported success rate is between 25 and 88% with no reported decrease in incontinence [66, 67].

OTSC clip—A C-shaped memory Nitinol alloy OTSC clip (Ovesco AG, Tubingen, Germany) is put on the internal opening of the fistula-in-ano like a claw in a bid to close the opening permanently. After a few weeks, the clip is removed. The reported success rate is between 25 and 88% with minimal loss of incontinence [68, 69].

Stem cells—These are new weapons in the armamentarium against complex fistula-in-ano. These can be autologous or allogeneic and can be adipose-derived or bone marrow-derived. Stem cells are given as a direct injection or given with fibrin glue or fistula plug. The latter helps to keep the stem cells together in the fistula tract. The reported success rate is between 46 and 69% with no impact on continence [42, 70–73].

Video-assisted fistula treatment (VAAFT)—In this procedure, a video endoscope is used. The fistula tracts are evaluated under vision by endoscope; all the tracts are cauterized by electrocautery under vision and then thoroughly washed. The internal opening is closed with a suture ligation or with a stapler device. The reported success rate is between 66 and 92% with net proportional cure rate of about 76% and minimal rate of incontinence [38, 74, 75].

Ligation of intersphincteric fistula tract (LIFT)—In this procedure, the intersphincteric plane is opened up and the fistula tract in the intersphincteric plane ligated and cut. The tracts external to the sphincter complex are curetted or cored out. A variation, BioLIFT procedure, has been reported in which LIFT is supplemented with insertion of bioprosthetic plug. The reported success rate of LIFT procedure is between 42 and 92% and the risk of incontinence between 0 and 6% [37, 76–84].

Transanal opening of intersphincteric space (TROPIS)—In this procedure, the tract in intersphincteric space is "deroofed" or opened from inside the anal canal (transanal route) [85, 86]. To achieve this, the mucosa and internal sphincter over the intersphincteric tract are incised with electrocautery. This not only destroys the infected crypt gland but also opens the tract in intersphincteric space which is then allowed to heal by secondary intention. The main aim of this procedure is to eradicate the sepsis present in intersphincteric plane and achieve fistula healing without doing any damage to the external sphincter. This is achieved by removing sepsis on both sides of the external sphincter so that both sides heal well. Sepsis eradication "inside the external sphincter" is done by transanal opening up of intersphincteric space (as described above), and sepsis "outside the external sphincter" is removed by curetting or coring out the external tracts [85, 86]. The success rate is between 86 and 95% in complex fistulas with no significant deterioration in continence on long-term follow-up [34, 40, 85–92].

Fistulectomy with primary sphincter repair (FPR)—In this procedure, the fistula tract including the internal opening is cored out completely, and to achieve this, the part of the sphincters (internal as well as external sphincter) below the tracts is divided. Once the complete fistula is excised, the divided sphincter is reconstructed by primary repair. The reported success rate is between 80 and 95% with incontinence rates between 6 and 14% [93, 94].

4.1.5.3 Choice of Procedures

Simple Fistula: Low Fistula (Involving Less Than One-Third of External Sphincter)
Fistulotomy remains the gold standard with success rate ranging from 88 to 100% [35, 44]. No other procedure has a success rate close to fistulotomy in simple fistulas [35, 44].

Complex Fistula: Low Fistula (Involving More Than One-Third of External Sphincter)
Complex anal fistula is one disease which is neither fully understood nor satisfactorily managed even today. However, a key breakthrough has been achieved in the understanding of the pathophysiology and hence management of complex fistulas. The detailed analysis of existing procedures like fistulolomy [35], fistulectomy with primary sphincter repair (FPR) [94], advancement flap, and various procedures innovated during the last decade like anal fistula plug (AFP) [1], ligation of intersphincteric fistula tract (LIFT) [84, 95], video-assisted anal fistula treatment (VAAFT) [38], and transanal opening of intersphincteric space (TROPIS) [40] helped to understand the three cardinal principles which are prerequisite to fistula management. If these principles are followed, then it is possible to achieve high cure rate in complex anal fistulas.

4.1.6 Cardinal Principles of Fistula Management

The three cardinal principles discussed below—ISTAC, DRAPED, and HOPTIC—are logical and derived from the basics principles of the wound healing [96, 97]. These principles fill the void in the understanding of complex anal fistula but were perhaps completely ignored till date. The procedures which take care of these three principles are expected to have a high success rate in complex anal fistula, and the procedures which ignore these principles would have high failure rates [96, 97].

1. *ISTAC: Intersphincteric Tract Is Like an Abscess in a Closed Space* [96, 97].

The fact which seems to have been missed/ignored over the years is the significance of the tract/sepsis in the intersphincteric space [7]. Almost all complex fistulas have an element of intersphincteric extension [7]. The sepsis in the intersphincteric space is quite similar to an abscess in a closed space (Fig. 4.2) [87]. This principle, *i*nter*s*phincteric *t*ract is like an *a*bscess in a *c*losed space (ISTAC), needs to be addressed to achieve high cure rate in complex anal fistulas [87].

2. *DRAPED: Draining All Pus and Ensuring Continuous Drainage* [96, 97].

Abscess anywhere else in the body cannot be treated by antibiotics alone or single-time aspiration of pus followed by antibiotics. It is treated by adequate drainage and deroofing at the same time. Deroofing is done to ensure continuous

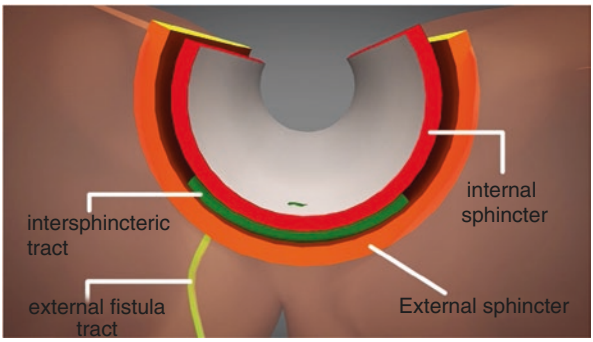

Fig. 4.2 ISTAC principle—intersphincteric tract is like an abscess in a closed space [96, 97]

drainage and avoid collection during the postoperative (healing) period [87]. Only when the cavity remains empty throughout the postoperative period that proper healing by secondary intention takes place. So, *dr*aining *a*ll *p*us and *e*nsuring continuous *d*rainage (DRAPED) is the basis of treating an abscess in any part of the body and is equally applicable in treating complex anal fistulas [87].

3. *HOPTIC: Healing Occurs Progressively Till It Is Interrupted Irreversibly by a Collection* [96, 97].

Another important point is that once the abscess is adequately drained and the wound is healing by secondary intention, any collection of pus in the wound would stop the healing process irreversibly. The reason behind this principle—*h*ealing *o*ccurs *p*rogressively *t*ill it is *i*nterrupted irreversibly by a *c*ollection (HOPTIC)—is not difficult to understand. During healing phase, even a single episode of collection is perceived as a danger by the rapidly healing tissues. This leads to immediate cessation of the healing process followed by the formation of a fibrous wall. The latter is formed to prevent spread of sepsis into the blood vessels of the advancing granulation tissue [96, 97]. A Unfortunately, this step is irreversible. Once the fibrous wall formation has been initiated, then even the removal of the causing factor (drainage of the collection) doesn't help. The fibrous wall though formed by the body cannot be removed by the body, and the patient then needs to be operated again to remove the fibrous wall. This phenomenon is similar to pulmonary fibrosis or liver cirrhosis where fibrosis is initiated by the body for its benefit, but the whole process becomes irreversible and ultimately becomes troublesome for the body itself.

4.1.7 Application and Relevance of these Principles in the Management of Complex Anal Fistulas

Once the concepts of ISTAC (*i*nter*s*phincteric *t*ract is like an *a*bscess in a *c*losed space), DRAPED (*dr*aining *a*ll *p*us and *e*nsuring continuous *d*rainage) and HOPTIC (*h*ealing *o*ccurs *p*rogressively *t*ill it is *i*nterrupted irreversibly by a *c*ollection) are

analyzed together, it becomes easy to understand as why most of the newer sphincter-saving procedures innovated during the last two decades do not seem to work well in complex fistulas [96, 97]. These newer sphincter-saving procedures concentrate on treating/debriding the external fistula tracts and closure of the internal (primary) opening. But these procedures do not address the issue of intersphincteric tract is like an abscess in a closed space (ISTAC) or draining all pus and ensuring continuous drainage (DRAPED). Therefore, most of these procedures like anal fistula plug (AFP) [1], video-assisted anal fistula treatment (VAAFT), over-the-scope clip (OTSC) closure, fibrin glue, and fistula-tract laser closure (FILAC) have healing rate of only 25–75%. On closer analysis, the majority of fistulas in the studies utilizing these new procedures were simple and low [1, 38]. Fistulotomy in such fistulas has a cure rate of up to 94–98% [35]. The success rate of these new procedures in a cohort of only complex anal fistulas has not been studied but is expected to be much lower [96, 97].

Ligation of intersphincteric fistula tract (LIFT) procedure, by ligating the intersphincteric tract, takes care of the ISTAC principle but fails to follow the DRAPED principle as the intersphincteric space is not deroofed to ensure continuous drainage in the postoperative period [87]. Therefore, LIFT has moderate success rate in complex fistulas [37, 76–84].

The only procedures which take care of both these principles are fistulectomy with primary repair (FPR) and transanal opening of intersphincteric space (TROPIS) [7]. FPR by excising the complete fistula tracts including intersphincteric tracts works in a manner similar to excision of the abscess. Therefore, though technically demanding and entailing extensive dissection, FPR works well in complex fistulas (healing rate 88–95%) [94]. TROPIS is a relatively new procedure in which the intersphincteric space is opened (deroofed) in the rectum through the transanal route [34, 40]. The external tracts are curetted and cleaned. As TROPIS procedure takes care of both ISTAC and DRAPED principles, its success rate is also 90–95% in complex fistulas [34].

Fistulotomy, by laying open all the fistula tracts including the intersphincteric component and keeping them open in the postoperative period, also takes care of both ISTAC and DRAPED principles [35]. Therefore, fistulotomy has a very high success rate (up to 95–98%), though it can understandably be done in only low fistulas [35].

4.1.8 Special Scenarios: Anal Fistulas

4.1.8.1 Anal Fistula with Tuberculosis

Apart from cryptoglandular fistula-in-ano, in Indian subcontinent, TB is the most common cause of anal fistula than any other associated disease. Extrapulmonary TB accounts for about 20% of all types of TB patients, and among these, perianal TB occurs in about 0.7% of them [98]. TB can not only masquerade as Crohn's disease

and other granulomatous diseases but can also lead to recurrent and refractory perianal fistula disease [2, 4, 99]. The analysis of the data in a recently published systematic review showed that the incidence of TB-infected fistula was 2.3–16% in the developing countries (endemic regions) and 0.3–1.2% in the developed countries [100–104]. Tuberculosis was significantly more common in complex fistulas vs simple fistulas (20.3% vs 7.2%, $p = 0.0002$) [3, 105]. Polymerase chain reaction (PCR) has been shown to be significantly more sensitive to detect TB in fistula tract and pus samples as compared to Xpert (gene expert) and histopathology [105].

TB infection may not be detected in the first sample [105, 106]. The need to send multiple samples to confirm TB in fistula is recognized [105, 106]. In a recently published large study, multiple additional samples (tissue and/or pus) were sent in 106 patients out of which 14 tested positive for TB [3]. This study found that TB was significantly much more common in complex fistulas (20.3%) as compared to simple fistulas (7.2%) [$p = 0.0001$]. It was also highlighted that up to 44–100% fistula patients having concomitant TB had recurrent fistula [3] and 13–80% of fistula had multiple tracts [3, 4, 100–102, 106, 107].

A high index of suspicion needs to be kept, and multiple samples should be sent in patients who have nonhealing of fistula, have complicated or progressive course even after surgery or have delayed recurrences [106]. PCR has quite high sensitivity to detect TB bacilli as it detects both dead and live bacteria. Therefore, this test should always be correlated with the clinical picture [3]. A positive PCR along with a background of nonhealing of fistula, development of newer tracts/abscesses, or delayed recurrence (after 3–6 months of the healing of the initial wound) would make a strong case for starting ATT [3, 105].

There could be several reasons for the higher association of TB with complex fistulas [3]. TB is not easily detected, which may lead to more recurrences, and therefore, the fistula infected with TB keeps on spreading and becomes more complex [3]. Another reason for the higher association of TB with complex fistulas could be that first-line antibiotics routinely prescribed to fistula patients are effective against the usual pathogens in anal fistulas (gram-negative bacteria and anaerobes) but are not effective against TB bacilli [3]. Therefore, untreated TB infection in these fistulas leads to unchecked progression of the fistula [3]. In addition, the treatment of TB is quite long (a minimum of 6 months). Due to this, the compliance is poor leading to the emergence of multidrug-resistant TB and further spread of disease [3]. Lastly, acute pyogenic abscess causes severe pain and toxemia which literally forces the patient to get urgent treatment. On the other hand, TB abscesses usually present as a “cold abscess,” which has minimal symptoms. The disease has a slow indolent progressive course. Due to this, patient keeps ignoring the disease process until it is quite advanced [3].

The patients having associated TB are treated with standard four-drug antitubercular therapy (ATT) prescribed for 6 months [3, 4, 108]. The regimen of HRZE for 2 months + HR for 4 months (H, isoniazid 5 mg/kg; R, rifampicin 10 mg/kg; Z, pyrazinamide 25 mg/kg; E, ethambutol 15 mg/kg body weight) is sufficient to treat most patients [3, 4, 108]. However, it is recommended that patients with a complex

fistula are also administered a deep intramuscular injection of 750 mg streptomycin (in the gluteus maximus muscle or mid-lateral thigh) once a day during the first 2 months of antitubercular therapy along with HRZE. This leads to better response in complex fistulas [3, 4, 108]. Liver function tests should be obtained before commencing the therapy and then monitored at monthly intervals.

4.1.9 Anal Fistula with Acute Abscess

Conventionally, it was taught that in a patient presenting with acute anorectal abscess with or without pre-existing fistula, a two-stage procedure should be performed. The abscess should be drained in the first sitting, and once the sepsis is under control, then the definitive surgery for fistula should be undertaken. However, the latest evidence points out that definitive fistula surgery can be done on the initial presentation in patients of acute abscess with comparable success rate and without any increase in risk of incontinence [31, 92, 109, 110]. This significantly decreases the morbidity. But surgical expertise and proper radiological assessment (by TRUS or MRI) are prerequisite before planning for the definitive surgery on initial presentation [31].

4.1.10 Anal Fistula with Non-locatable Internal Opening

The fistula recurrence rate is very high when the internal opening (IO) cannot not be clearly identified (IO-non-locatable) [111–113]. There are three usual ways to locate IO—clinical examination (palpating the area of maximum induration, pulling the external opening and noticing the point of dimpling in the anal canal and visual inspection of the anal canal), intraoperative injection of colored solution through the external opening to notice its egress from the anus, and a detailed MRI analysis.

When these three usual methods fail to locate IO, a three-step protocol (Garg protocol) helps to manage such fistulas effectively [92, 114]. First, preoperative MRI is assessed again [114]. Second, in non-horseshoe fistulas, the site where the fistula tract approached closest to the sphincter complex is identified [114]. The IO is assumed to be located at that site, and the fistula is managed accordingly [114]. Third, in horseshoe fistulas with non-locatable IOs, the IO is assumed to be in the midline (posteriorly in posterior horseshoe or anteriorly in anterior horseshoe fistulas) [114]. Garg protocol has been shown to be quite effective. In a large cohort of anal fistula patients, this protocol was followed and long-term follow-up was done [114]. The main outcome parameters (fistula healing rate and objective incontinence scores) in IO-locatable ($n = 546$) and IO-non-locatable ($n = 154$) groups were comparable (healing rate of 89% vs. 90% in IO-locatable vs. IO-non-locatable groups, respectively, $P = 0.55$) [114].

4.2 Hemorrhoids

The epidemiological data points toward a hemorrhoid prevalence of 13–36% within general population [115]. However, based on screening colonoscopy data, about 38% of the population had hemorrhoids, out of which only 44% reported symptoms [116].

4.2.1 Internal Hemorrhoids

Anatomically, hemorrhoidal columns are normal clusters of vascular and connective tissue, smooth muscle, and overlying epithelium that exist in the left lateral, right anterior, and right posterior anal canal and play an important role in providing continence. They can become pathologic when they engorged. Internal hemorrhoids are anatomically situated proximal to the dentate line, are covered in columnar epithelium, and are supplied by visceral innervation [116].

The *classification* of internal hemorrhoids is clinical and is as follows:

- *Grade 1:* hemorrhoids do not prolapse; they occasionally bleed or are detected incidentally during colonoscopy.
- *Grade 2:* prolapse with straining but get reduced spontaneously.
- *Grade 3*: require manual reduction to reduce prolapse.
- *Grade 4*: are irreducible.

4.2.2 External Hemorrhoids

External hemorrhoids are perianal subcutaneous venous plexuses, anatomically distal to the dentate line, somatically innervated, and covered by squamous epithelium. External hemorrhoids can also become pathological when these venous plexuses spontaneously rupture, resulting in a painful subcutaneous hematoma or "thrombosed external hemorrhoids." [116]

4.2.3 Etiology

In the beginning, the etiology of hemorrhoids was thought to be caused by portal hypertension; however, the latest understanding is that symptomatic hemorrhoids occur with deterioration of the tissues that support the anal cushions, causing abnormal downward displacement and venous dilation [117–119]. This process usually gets exacerbated by lifting, straining, and prolonged sitting. Other risk factors include a low-fiber diet and constipation, though epidemiological studies have shown that hemorrhoids and constipation may have different distributions among

the population [120, 121]. So it has been proposed that spending more time in the toilet due to several reasons (constipation, mobile phone usage, or newspaper reading) is one of the key factors in development and progression of hemorrhoids [122].

4.2.4 Medical Treatment

Symptomatic early hemorrhoids tend to be self-limiting and often respond well to usually recommended conservative medical treatment: increasing fluid and fiber intake, regular exercise, avoiding constipation and straining, and spending less time in the toilet. A meta-analysis of seven randomized trials comparing fiber supplementation (7–15 g/day) to no fiber showed that fiber supplementation decreases bleeding symptoms by 50%, but had little effect on prolapse, pain, and itching from hemorrhoids [123]. There is no evidence to support the use of popular topical over-the-counter remedies like Preparation H or topical corticosteroids [124, 125]. However, recent research highlighted that when specific objective goals are set for the patients (TONE) and fiber is supplemented in sufficient dosage and given with adequate amount of water, then it is possible to avoid hemorrhoidal symptoms and progression in early as well as advanced hemorrhoids [122, 126].

4.2.4.1 TONE Concept

The role of fiber had been studied primarily in early hemorrhoids and not in advanced hemorrhoids [123]. The reason for this could be that since fiber was shown to be only moderately effective in early hemorrhoids, its efficacy in advanced hemorrhoids was doubted [123]. Secondly, even in early hemorrhoids, the long-term beneficial effects of fiber was unknown as most of the studies had short-term follow-up (1–3 months) [127–129].

The efficacy of fiber had perhaps been underestimated in the past as in most studies, the required emphasis was perhaps not given on the dose of the fiber and the amount of water to be taken along with it [122, 126]. The dose of fiber (7–15 grams per day) given to the patients in these studies was less than adequate [128, 130]. As the daily requirement of fiber is 25–38 grams (women, 25 g/day; men, 38 g/day) and an average adult takes less than 15 grams of fiber per day [122, 131], the fiber supplement should be at least 20–25 grams. Secondly, it is well known that fiber is effective when taken with adequate amount of water [132–134]. If water intake with fiber is not adequate, then it would be less effective and might cause paradoxical constipation [122]. Aforementioned could be the reason that fiber was shown to be effective in only early hemorrhoids and that too on a short-term basis. Therefore, when 20–25 grams of fiber was prescribed to be taken along with 600 ml of water, it proved to be much more effective [122, 126, 135].

Deranged defecatory habits (DDH)—spending prolonged time during defecation, increased straining while defecation, and increased frequency of motions—are the root causes of hemorrhoid initiation, hemorrhoid progression, and hemorrhoid

rupture (bleeding) [122, 126]. If these root causes of hemorrhoids (DDH) are corrected, then the hemorrhoidal progression would stop, and additional symptoms (bleeding or thrombosis) could be largely prevented [122, 126]. On the other hand, if DDH are not corrected, then the disease would continue to progress or recur even after treatment of hemorrhoids with an outpatient procedure or surgery. The latter is thus only the symptomatic treatment of the disease, while correction of DDH is the actual long-term treatment of the disease.

Ironically, DDH are seldom corrected. The reasons for this are:

1. Though patients are usually advised to correct DDH by physicians, yet the exact goals (end points) of corrected defecatory habits are seldom communicated to the patients [122].
2. Along with knowing the exact goals, it is essential that intake of an optimum amount of fiber with sufficient water is ensured so that these goals can be achieved. This point is not adequately stressed by many physicians [122, 126, 135].

Both these points were summated as TONE concept [122, 126, 135]:

- *T*—*T*hree minutes at defecation (spending 3–5 minutes in toilet).
- *O*—*O*nce a day (frequency of defecation to be once a day)
- *N*—*N*o straining (no excessive straining while defecation, not to take newspaper or mobile phone in the toilet).
- *E*—*E*nough fiber (5–6 teaspoonfuls of fiber with 500–600 ml of water). The first three components of therapy (TON) would become possible only if the step is correctly done [122, 126, 135].

In this concept, TON indicates the goals (end points) of corrected defecatory habits, and E indicates the required amount and right way to take fiber so that goals (TON) could be achieved. TONE concept stops progression of existing hemorrhoids and prevent their rupture (bleeding) in majority of cases. It has been shown that when TONE was followed, surgery was prevented in more than 90% of patients with even advanced hemorrhoids [122, 126, 135, 136].

4.2.5 Office Procedures

There are several office procedures rubber band ligation (RBL), injection sclerotherapy, infrared coagulation, radiofrequency ablation, etc. A meta-analysis of 18 trials comparing rubber band ligation, sclerotherapy, and other office procedures for hemorrhoids showed that rubber band ligation had a better cure rate for grade I–III hemorrhoids, with no difference in complication rates [137]. Rubber band ligation tended to cause more pain initially, but was less likely to be followed by recurrence of symptoms [137]. Infrared coagulation and sclerotherapy were more likely to require additional procedures compared to rubber band ligation [137].

4.2.5.1 Rubber Band Ligation

Rubber band ligation was described by Barron in 1963. It is the most commonly performed office procedure for bleeding grade II and III hemorrhoids, not responsive to conservative management [137]. During this procedure, a rubber band is placed around a hemorrhoidal column, causing tissue necrosis and fixation to the mucosa. Necrosis usually occurs in 3–6 days, followed by ulceration and healing in several weeks. Rubber band ligation should not be performed on external hemorrhoids because of their somatic innervation. Other contraindications include patients on anticoagulation or with a coagulopathy, as there can be risk of significant bleeding. The procedure is done as an outpatient procedure, with the patient in a left lateral or jack-knife prone position. It doesn't require any kind of anesthesia. An anoscope is used to visualize the hemorrhoids, and rubber bands are deployed at least half a centimeter above the dentate line. It is important to confirm that there is no pain before and after placement. The reported complications include pain (most common), urinary retention, delayed bleeding, and perineal sepsis. A large retrospective review of 805 patients and 2114 rubber band ligation procedures found an overall success rate of 80%, with complications such as bleeding (2.8%), thrombosis of external hemorrhoid (1.5%), and bacteremia (0.09%) [138].

4.2.5.2 Sclerotherapy

Sclerotherapy is second most commonly done office-based procedure for treating internal grade I and II hemorrhoids. This is an especially good treatment and, unlike rubber band ligation, can even in done for the patients on anticoagulation or with coagulopathy. Like rubber band ligation, the procedure can also be performed without the need of any anesthesia. The hemorrhoids are visualized on anoscope, and a sclerosant, such as 5% phenol in vegetable oil (usually almond oil), ethanolamine, quinine, or hypertonic saline, is injected in them [124]. This causes fibrosis and fixation of the tissue to the anal canal, thus obliterating the redundant hemorrhoidal tissue. There are several reported complications especially if injections are given repeatedly. The most common complications are pain (if injection site is too low or too deep), excessive bleeding (in patients on anticoagulants), and development of submucosal or even extensive perianal sepsis.

4.2.5.3 Infrared Coagulation

Infrared coagulation is a variation of sclerotherapy where hemorrhoids are sclerosed using an infrared coagulator [137]. The procedure is performed similarly, but instead of sclerosant, an infrared coagulator is applied to the base of the hemorrhoids for 2 sec, 3–5 times, until white blanched mucosa is seen, eventually causing scaring and retraction of the prolapsed mucosa [137].

4.2.6 Surgical Management

Surgical treatment is indicated for grade III or IV internal hemorrhoids and for thrombosed external hemorrhoids with persistent symptoms.

4.2.6.1 Thrombosed External Hemorrhoids

Excision is recommended within the first 48 h of symptoms for thrombosed external hemorrhoids though most of these resolve on conservative management. Incision and drainage is ineffective, and complete excision of the hemorrhoid with the associated external skin is advised. This procedure can be done as an outpatient procedure or in an emergency care setting with local anesthesia. A large review of 231 patients comparing excision to nonoperative treatment of thrombosed external hemorrhoids showed that excision symptoms resolved more rapidly (average of 3.9 days vs 24 days in the nonoperative group) and were less likely to recur [139].

4.2.6.2 Acute Hemorrhoid Crisis

Acute hemorrhoid crisis is rare, and will present as ulcerated or necrotic hemorrhoids on examination. This occurs when internal hemorrhoids prolapse and become incarcerated as a result of sphincter spasm. This condition warrants hospital admission. It is not uncommon to have concurrent thrombosed external hemorrhoids. Most patients with acute hemorrhoid crisis benefit from hospitalization and conservative management, including bowel rest, pain control, antibiotics, and sitz baths [140]. Necrotic hemorrhoids and perineal sepsis are indications for urgent exploration and excision.

4.2.6.3 Hemorrhoidectomy

There are two approaches to hemorrhoidectomy: the Ferguson (closed) and the Milligan-Morgan (open) technique. Both use elliptical incisions starting at the perianal skin; the Ferguson technique closes the wound primarily, while in the Milligan-Morgan technique, the wound is left open. The vital step of the procedure is to ensure that the hemorrhoidal tissue is dissected off the sphincter before the vascular pedicle is ligated. One to three columns may be excised. Most surgeons prefer Milligan-Morgan technique for gangrenous hemorrhoids. There is no difference in the resolution of symptoms between the two approaches, but the Ferguson technique leads faster wound healing [141]. The most serious long-term complication is incontinence due to sphincter injury. One study demonstrated sphincter muscle fibers in up to 15% of hemorrhoidectomy specimens [142]. Since the normal hemorrhoidal cushions play an important role in maintaining continence,

hemorrhoidectomy can cause changes in continence postoperatively, even without direct injury to the sphincter [143]. Anal stenosis is a late complication of hemorrhoidectomy, and is related to the amount of tissue excised [143].

To reduce bleeding and pain after conventional surgical hemorrhoidectomy, utilization of vascular sealant devices such as LigaSure and harmonic scalpel has been advocated [143].

4.2.6.4 Stapled Hemorrhoidopexy

Stapled hemorrhoidopexy, also known as procedure for prolapsing hemorrhoids (PPH), is another surgical method for grade II and III hemorrhoids that uses a stapler device to resect and, more importantly, fixate tissue to the rectal wall. The critical step of the procedure is making a circumferential purse string suture in the submucosa about 3–4 cm from the dentate line that does not include any sphincter muscle. If the purse string is low in the rectum, it can include the dentate line in the staple line and cause intense postoperative pain, and if the purse string is too deep, the stapler may make a full-thickness excision through the rectal wall. This could be followed by abscess or fistula, which may require surgical intervention [140]. Complications of stapled hemorrhoidectomy include bleeding, sphincter muscle injury, anastomotic line dehiscence, anal stenosis, proctitis due to retained staples, and rectovaginal fistula [144, 145]. Moreover, this procedure, unlike surgical hemorrhoidectomy, doesn't deal with external hemorrhoids. A large meta-analysis comparing open hemorrhoidectomy to stapled hemorrhoidopexy showed that stapled hemorrhoidopexy patients had less postoperative pain during bowel movements, earlier bowel movements post-op, shorter hospital stays, and fewer narcotic requirements [146]. This study showed no differences in post-op complications, but the stapled group had more frequent recurrence of prolapse at 2 years [146]. However, there is evidence to suggest that recurrence rate after stapled hemorrhoidectomy can be reduced by taking a horizontal mattress suture at the staple line [147, 148]. After that, several meta-analyses have confirmed that stapled hemorrhoidopexy has higher rates of recurrence than hemorrhoidectomy [149–151]. Overall, the use of stapled hemorrhoidopexy has declined significantly after the initial enthusiasm [149–151].

4.2.6.5 Doppler-Guided Hemorrhoidal Artery Ligation

Doppler-guided hemorrhoidal artery ligation (DGHAL), also called transanal hemorrhoidal dearterialization (THD), is a non-excisional surgical method to produce hemorrhoidal shrinkage that utilizes a Doppler probe to identify the six main feeding arteries in the anal canal and ligates the ones feeding the symptomatic hemorrhoids. The redundant tissue is plicated to perform a mucopexy during the procedure. Initial studies showed promising results for this method, but randomized trials have demonstrated more mixed results [152, 153]. Two randomized trials comparing Doppler-guided hemorrhoidal artery ligation to open hemorrhoidectomy showed

less postoperative pain in the hemorrhoidal artery ligation group and no significant difference in recurrence at 1 year [152, 153]. In contrast, a third randomized trial showed no difference in postoperative pain, complications, or recurrence between the hemorrhoidal artery ligation and open hemorrhoidectomy groups [154].

It remains unclear what the best treatment for hemorrhoids is, as there is significant heterogeneity in the methodologies applied and the study end points examined in all the aforementioned studies [124]. Additionally, surgeon bias affects the techniques used, and indications depend on the operators and their experience [124]. Another confounding factor in these studies is that patients and providers often define recurrence differently after treatment, but the European Society of Coloproctology has recently developed a Core Outcome Set to address this shortcoming of the current literature [155]. A large meta-analysis of 98 randomized clinical trials has concluded that, although *hemorrhoidectomy is associated with higher postoperative pain than hemorrhoidal artery ligation (DGHAL) and stapled hemorrhoidopexy, but it yields the lowest recurrence rates. Overall, surgical hemorrhoidectomy should be considered the standard for surgical care of hemorrhoidal disease, but surgical treatment should be tailored to each patient's symptoms and exam findings* [156].

4.3 Anal Fissure

An anal fissure is a linear tear in the anal mucosa or anoderm, usually extending from the dentate line to the anal verge. Anal fissures are common, and occur in all age groups, but appear to be more common in young and middle-age groups [127]. Most fissures occur at the posterior midline (90%) [157–159]. Anterior midline fissures occur more commonly in females than males. In females, 10–25% of fissures are anterior, whereas in males, only 1–5% are anterior [157, 159]. Anterior and posterior midline fissures can also occur concomitantly in about 3% of cases [159]. A lateral fissure is uncommon and should raise concern for a secondary cause like inflammatory bowel disease, tuberculosis, human immunodeficiency virus, trauma, syphilis, etc [160]. The cardinal symptom of anal fissure is remarkable pain, and this can negatively impact quality of life [160].

4.3.1 Pathophysiology

There are several reasons postulated to cause anal fissure. Conventionally, anal canal trauma from hard stools or diarrhea was thought to be the prime culprit. However, constipation and hard bowel movements are not reported in all patients with fissures [158]. It is speculated that persistently high internal sphincter tone leads to chronicity of fissures [161]. Pain from the fissure triggers anal reflex which contributes to the increased sphincter tone [161]. These changes in tone may become pathological, and then persist for long periods of time. One study demonstrated that

internal sphincter biopsies taken at the time of internal sphincterotomy for chronic anal fissure had less nitric oxide present compared to internal sphincters from abdominoperineal resection specimens pointing toward increased sphincter tone's role in persistence of symptoms [162]. The persistent increased internal sphincter tone causes local ischemia that prevents the fissure from healing, creating a chronic wound. The inferior rectal arteries that supply the anoderm have to traverse through the internal sphincter. Studies have shown that the perfusion of the anoderm is inversely related to the pressure of the internal sphincter [163]. Angiography and cadaver studies have shown that there is a paucity of arterioles in the posterior midline anal canal that possibly explains the propensity for fissures to occur at this location [164, 165]. There is another entity of fissures associated with childbirth. This fissure develops due to shear forces from the baby's head during birth [157]. About 10% of chronic fissures in females, associated with difficult or instrumented deliveries, occur after childbirth, and are most common in the anterior midline [157]. Unlike other fissures, these fissures are not associated with increased sphincter tone, but have normal or even low tone. Therefore, sphincterotomy is not indicated for treatment of these fissures [166]. A peculiar reason highlighted recently as a cause of anterior fissure is usage of water-jet stream in bidet toilets. This is more common in India and Asian countries and is responsible for surge in anterior fissures even in male population [167–169].

4.3.2 Diagnosis

The diagnosis of anal fissure is usually clinical with no need for any investigation. Patients usually present with anal pain, which is usually quite severe and remain for several hours after bowel movements. Occasionally, there may be associated bleeding with bowel movements. However, unlike hemorrhoids where the bleeding is usually "splash in the pan," the bleeding in fissure is usually "streaking of the stools." A fissure is diagnosed upon a gentle per-rectal examination, although this may be difficult because of severe pain and internal sphincter spasm. Chronic fissures develop indurated edges, which may have visible sphincter muscle at the base with associated hypertrophic papilla proximally and sentinel tags distally [158].

4.3.3 Classification and Treatment Algorithm

The fissure-in-ano can be classified on the basis of duration of onset of symptoms and clinically assessed anal tone [170, 171]. This classification can clearly guide regarding the management of the anal fissure and clears a lot of confusion prevailing over the classification of the anal fissures [170, 171]:

- Acute fissure <6-week duration with high anal tone (DRESS score—4–5).

- Chronic fissure >6-week duration with normal/low anal tone (DRESS score—1–3).
- Acute-on-chronic fissure >6-week duration with high anal tone (DRESS score—4–5).

The resting anal tone can be assessed clinically on an objective scale—DRESS—the digital rectal examination scoring system [172].

(0, no pressure, open/patulous anus; 1, very low pressure; 2, mildly decreased; 3, normal; 4, elevated, snug; 5, extremely tight) [172].

4.3.4 Medical Treatment

Treatment of anal fissures starts with conservative treatments which include stool softeners, fiber supplementation, sitz baths, and topical lidocaine gel for pain control. Stool softeners and lidocaine gel together will heal 8–51% of fissures, with most studies showing healing rates of 16–31% in acute and chronic fissures [157]. Almost half of acute fissures will heal with sitz baths and fiber, with or without lidocaine gel [159]. The effect of topical steroids or lidocaine gel in healing fissures is equal to or worse than sitz baths and fiber [159]. Lidocaine by itself does not appear to contribute to healing of fissures, but provides symptom relief [173]. The goal of medical treatment of anal fissures is to decrease the internal sphincter tone and allow healing. Topical nitrate use leads to healing of chronic anal fissures in about 50% of patients, and demonstrates 13.5% more improvement in healing as compared to placebo [159]. Up to 50% of fissures healed with nitrates may have recurrences [159]. The topical nitrates commonly used are isosorbide dinitrate and glyceryl trinitrate. However, nitrates were associated with significant incidence of headache [159]. Therefore, after the advent of topical calcium channel blockers, the usage of nitrates has decreased significantly [159]. A randomized double-blind multicentric trial comparing nifedipine gel to topical hydrocortisone and lidocaine found that the nifedipine treatment healed fissures in 95% of patients, compared to 50% in the control treatment group [174]. Additionally, anal manometry demonstrated that nifedipine decreased the resting anal pressure by 30%, whereas there was no change in the control group [174].

4.3.5 LOABAC (Local and Oral Antibiotic and Avoidance of Constipation) Treatment

The reason for initiation of a wound (fissure) in acute fissure-in-ano and the persistence of the same in chronic anal fissure is perhaps repeated shearing trauma, most commonly due to constipation (hard fecalith). In chronic cases, superimposed

subclinical infection in the lesion also adds to the symptoms [175–177]. A large study found a subcutaneous tract at the base of the chronic fissure in a large proportion of chronic fissure patients and hypothesized that the subclinical infection could be a contributing reason for the persistence of symptoms in chronic fissure-in-ano [176]. The principle behind LOABAC is that by eradicating the subclinical infection by giving an oral course of antibiotics, preventing reinfection by applying a topical antibiotic cream on the fissure, and strictly avoiding constipation (recurrent episodic shearing trauma) for at least 6 months, the fissure would heal [170, 171, 178]. However, this might not be effective in cases where the fissure had already deepened to form a fissure sinus or a fissure fistula [170, 171]. A recent study demonstrated that 87% (78/90) of chronic fissure-in-ano patients had their fissures healed with conservative treatment, were highly satisfied with the treatment, and required no further intervention [170, 171]. As mentioned above, this treatment helped prevent surgery in a large majority of patients with chronic fissure-in-ano except the fissures which had already deepened to form fissure sinus or a fissure fistula [135, 170, 171]. The latter required surgical intervention.

4.3.6 Botulinum Toxin (Botox) Injection

When the conservative management with topical ointment fails, another available option is injection of botulinum toxin (Botox) into the internal sphincter. Botox is associated with healing rates ranging from 27 to 96% [157]. The most common reported side effect is temporary incontinence, mainly to flatus, in up to 18% of patients [157]. A meta-analysis showed that Botox injection had no significant advantage over glyceryl trinitrate or placebo [173]. Overall, Botox injections have comparable healing rates as those of other topical agents when used as a first-line agent, but has better healing rates when compared to second-line agents [159, 179]. The main advantage of Botox over topical nitrates and calcium channel blockers is that its compliance is not patient-dependent as it does not require the patient to regularly apply cream in the painful area and also doesn't cause unpleasant headaches [180, 181]. However, there is no consensus over the ideal dose, preparation, or injection site of Botox [159]. A meta-analysis comparing Botox to sphincterotomy showed that though Botox had lower healing rates than sphincterotomy, it had lower rates of incontinence than sphincterotomy [182]. A Cochrane review of nonsurgical therapy for anal fissures, comprising of 77 studies with a total of 5031 participants, showed that glyceryl trinitrate is slightly but significantly better than placebo (48% healed vs 35%) [183]. Botox and calcium channel blockers were equivalent to glyceryl trinitrate in efficacy, but were associated with fewer side effects [183]. Though, overall, medical therapy were less efficacious than sphincterotomy but unlike sphincterotomy, medical treatments do not carry any risk of permanent incontinence [173, 183].

4.3.7 Surgical Management

4.3.7.1 Lateral Internal Sphincterotomy (LIS)

LIS is the surgical treatment of choice for acute as well as chronic fissures [159]. Several randomized studies show the superiority of LIS to nitrates, calcium channel blockers, and Botox [159]. LIS has healing rates of 88–100%, but is associated with incontinence rates of 8–30% [159]. Initially, it was reported that most of the associated incontinence is transient and does not extend beyond 2 months and the incontinence rate beyond 2 months is only 3–7% [157]. However, a large proportional meta-analysis of LIS with a follow-up of more than 2 years (range 2–10 years) in 22 studies ($n = 4512$) showed that LIS was associated with a long-term incontinence in 14% of patients. This included flatus incontinence in 9%, soilage/seepage in 6%, accidental defecation in 0.91%, incontinence to liquid stool in 0.67%, and incontinence to solid stool in 0.83% of patients [184].

Recurrence rate of fissure after LIS is 0–15% [157]. Traditionally, in LIS, the sphincterotomy was done up to the dentate line. To decrease incontinence after LIS, tailored sphincterotomy extending just proximal to the fissure has been shown to preserve sphincter, thereby decreasing incontinence rates [185]. Understandably, the more sphincter is cut, the higher is the risk of incontinence and the lower is the rate of recurrence [186]. LIS can be open or closed, but there is no significant difference in outcomes between open or closed LIS [159, 187]. Though LIS is considered as the first-line surgical treatment in patients without prior obstetrical injury, inflammatory bowel disease, prior anorectal operations, or sphincter injury [159], this is being challenged as more and more data is accumulating against the long-term safety of LIS.

4.3.7.2 Local Advancement Flaps

Local advancement flaps are the preferred surgical treatment for chronic anal fissures associated with normal or low anal pressures. The advancement flap can be anocutaneous or rectal flap. One study showed that anocutaneous advancement flap anoplasty led to healing of 94% of fissures without any deterioration in continence; the 6% fissures that recurred did so at a different location from the initial fissure [188]. Overall, advancement flaps are a safer approach to treat chronic anal fissure, with healing rates of 88–100% and incontinence risk of 0–6% [159]. However, flap failure occurs in 5–11% of patients and is the main complication of this procedure. Occasionally, flap edge ectropion can lead to mucosal discharge and perianal skin irritation. A flap can also be combined with sphincterotomy or Botox if there is associated spasm (acute on chronic fissure) [159].

4.3.7.3 Fissurotomy and Fissurectomy

Many fissures deepen to form subcutaneous tracts which harbors a smoldering infection [176]. Fissurotomy is the act of incising that tract to release the infection [176]. The wound is left open to heal by secondary intention. In a study of 109 chronic fissure patients undergoing fissurotomy, resolution of symptoms occurred in 98%, while the remaining 2% required sphincterotomy [176]. Fissurectomy is the excision of the chronic fissure wound, curettage of the base of the fissure, and excision of a sentinel pile, if present. Fissurectomy is associated with around 3% recurrence rate and a 6% rate of incontinence [189]. Fissurectomy and concomitant isosorbide dinitrate cream for chemical sphincterotomy resulted in all wound healing within 10 weeks in almost all patients and no evidence of internal sphincter injury [190]. Another study of fissurectomy plus Botox showed healing of wounds at 16 weeks in 93% of fissures, and improvement in symptoms in all the patients [191]. However, a Cochrane review found that sphincterotomy was less likely to result in treatment failure compared to fissurectomy, with a similar risk of incontinence [187]. So undoubtedly, LIS is still the standard surgical treatment for acute anal fissures with increased sphincter tone in which medical management has failed.

4.3.8 Treatment Algorithm of Anal Fissure

The classification discussed above sorts out a lot of confusion prevailing over the classification of the anal fissures [135]. An effective algorithm to treat anal fissures was published recently (Fig. 4.3) [170, 171].

4.4 Pilonidal Sinus Disease

4.4.1 Introduction

Pilonidal (pilus = hair, nidus = nest) sinus disease (PSD) is a common disease, affecting roughly 26 per 100,000 population [192]. It predominantly affects young males and is rarely seen before puberty or in later life [192]. It can cause repeated suppuration and pain. Risk factors for the condition include male gender, young age, mild to moderate obesity, hairiness, deep natal cleft, and poor hygiene [192, 193]. The exact etiology of pilonidal sinus disease is unclear; however, it is hypothesized that hormone changes lead to enlargement of hair follicles which block the pilosebaceous glands in the sacrococcygeal area [192]. Further the shape of the natal cleft facilitates the burial of the barbed shaped hairs into these sinuses, which

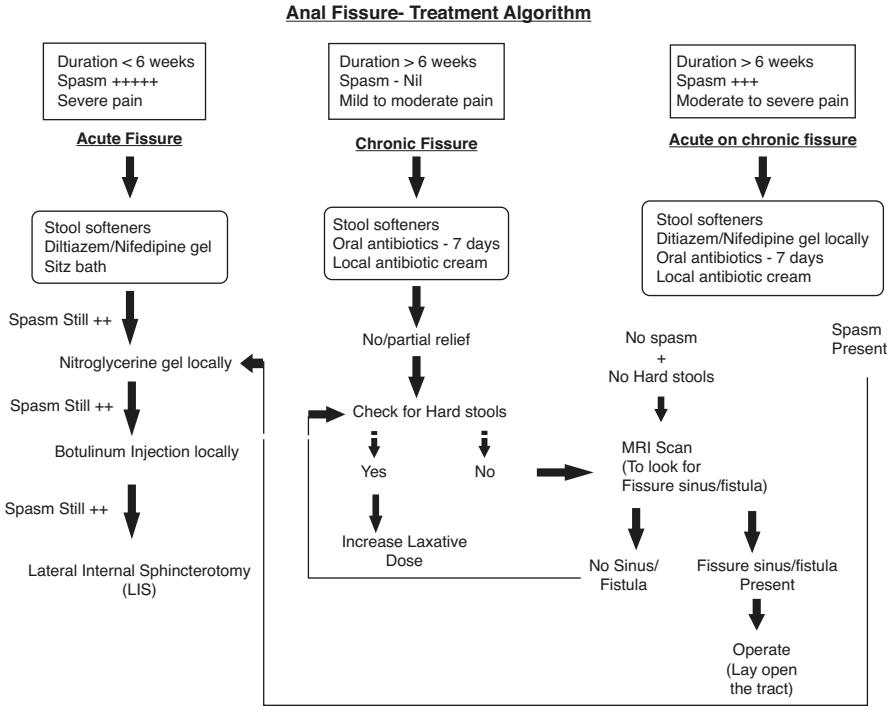

Fig. 4.3 Treatment algorithm for anal fissure

act as a foreign body to exacerbate the infection [192]. PSD can initially present as either an acute abscess or a discharging sinus. PSD can be associated with tuberculosis, and a recent study has shown that PSD and anal fistula can also coexist [108]. If the latter scenario is missed and not kept in mind, then it can lead to repeated recurrences of PSD [108]. Several different surgical techniques have been described for the primary treatment of pilonidal sinus disease, and current practice remains debatable and contentious.

When assessing the outcomes of various pilonidal treatment, there are many factors which need to be considered: [194, 195]

- Time to complete healing.
- Time to return to work/education.
- Cure rate/disease recurrence.
- Technical complexity of the procedure.
- Postoperative wound complications.
- Strategy to prevent long-term recurrences.
- Patient preference.

However, most studies failed to measure and record all these parameters. The various management options are as follows.

4.4.2 Asymptomatic Pit Treatment

For patients with asymptomatic pits, a conservative approach may be reasonable. Keeping the area hair-free and good, local hygiene should suffice in these cases. Studies have shown that most of these patients don't require any surgical intervention [196].

4.4.3 Acute Abscess Treatment

Earlier, some surgeons advocated wide en bloc excision even for those patients who presented an acute abscess. However, in a large study in 483 patients, disease recurrence rates following a first episode of incision and drainage are as low as 20% at 20-year follow-up [197]. Another study found similar recurrence rates in patients with acute pilonidal abscess treated with simple incision and drainage vs wide excision, but the average time to return to work for the latter group was much higher (7 vs 14 days) [198]. Therefore, there is little justification for the performance of wide en bloc excision for acute abscess presentations as it would result in overtreatment in a vast majority (more than 80% of patients), and therefore should be abandoned. Incision and drainage is recognized as the treatment of choice for acute pilonidal abscesses, and it can be performed safely under local anesthesia [199].

4.4.4 Chronic Disease Treatments

4.4.4.1 Phenolization of Pit Tracts

Phenol has sclerosant properties destroying epithelium and debris within the sinus and promoting sinus healing and was first described in 1964 in an ambulatory setting under local anesthetic [200, 201]. A systematic review of observational studies reported a mean recurrence rate of 12.6% at 2-year follow-up, a SSI rate of 8.7%, and a mean return to work of 2.3 days [202]. In a RCT of 140 patients, phenol injection was compared with excision with healing by secondary intention [203]. The risk of recurrence was similar between the phenol group (18.6%) and the excision group (12.9%) after an average follow-up period of 39.2 months. Complete wound healing occurred significantly faster in the phenol group (16.2 vs 40.1 days, $P < 0.001$). It should be noted that phenol should be avoided in patients with nut allergy or with previous known reactions to phenol usage. So, phenolization leads to faster healing but at the cost of higher recurrence rate.

4.4.4.2 Laying Open and Curettage under Local Anesthesia (LOCULA)

Laying open of all the involved sinus tracts with curettage may be adequate to achieve cure of the disease [204]. A recent study demonstrated a success rate of 97% with LOCULA procedure in cohort consisting of both pilonidal abscess and chronic pilonidal disease [199]. A large meta-analysis was performed in 2016 (13 studies, 1445 patients) which analyzed LOCULA [laying open (only deroofing, not excision) and curettage of sinus under local anesthesia] procedure to treat simple as well as complicated pilonidal disease [205]. The study reported a net proportion meta-analysis pool rate of 4.47% for disease recurrence (95% CI 0.029–0.063), 1.44% for complications (95% CI 0.005–0.028), 8.4 days to return to work (95% CI 5.23–11.72), and time to healing of 21–72 days. When compared with wide en bloc excision, a further meta-analysis found no significant differences in the rate of disease recurrence (RR 0.63, 95% CI 0.17–2.38; $P = 0.856$) [206], and wide excision offered no additional advantage. There was a significantly earlier return to work and lower postoperative pain scores with the laying open approach. This meta-analysis demonstrated that LOCULA has distinct advantages. It has high success rate, possible in all types of pilonidal disease (simple and complex), low complication rate, short operating time, and early return to normal routine and work. This procedure can be conveniently under local anesthesia as an outpatient procedure, and the patient requires no hospital admission [204, 205].

The recent evidence makes a strong case in favor of LOCULA procedure as a frontline procedure for pilonidal sinus, simple as well as complicated (recurrent disease, associated with abscess, concomitant tuberculosis, etc.) [204, 207–209].

4.4.4.3 Pit-Picking Techniques

Lord and Miller described tiny "pit-picking" excisions and cleaning of the sinuses in 1965, based on the theory that if the hairs are removed and free drainage allowed, then the pilonidal sinus will heal [210]. Later, *Bascom* incorporated a lateral abscess drainage incision into this procedure [211, 212]. This technique could be performed under the use of local anesthetic. However, a systematic review demonstrated a recurrence rate of 12% with "pit-picking procedures" [213]. The mean time to wound healing was 4–8 weeks and a wound complication rate of 2–8%. Though initially looked attractive, the procedure was associated with a higher disease recurrence rate.

4.4.4.4 Wide En Bloc Excision with either Primary Midline Closure or Healing with Secondary Intention

The conventional popular treatment of PSD involves the complete excision of midline skin pits and the associated sinus tracts via a wide en bloc excision. Debate still exists as whether the wound should be closed primarily in midline or left open to heal by secondary intention. The recurrence rate of 6–12% has been reported after

primary midline closure [214]. A meta-analysis of randomized controlled trials was published in 2008 [215].The study included 18 trials (n = 1573) that compared wound healing rates in open healing vs primary midline closure [215]. Open healing (n = 320) was found to have a lower risk of recurrence than primary closure (n = 353) (RR 0.39, 95% CI 0.23–0.66; $P < 0.001$) [215]. Patient who underwent open healing took longer to return to work compared with primary midline closure (mean difference of 8.56 days) [215]. In summary, wounds healed quicker when primary midline closure was performed, but this came at the expense of higher rates of disease recurrence.

4.4.5 Off-Midline Closure Techniques: Rotational Vs Advancement Flaps

The prime purpose of doing off-midline closure techniques was:

1. To prevent tension in the primary closure wound as happens in the midline closure.
2. To flatten the contour of the buttocks (natal cleft) with aim of decreasing long-term recurrences. As the buttock contour is flattened, there would be no need of periodic cleaning of hairs by the patient.

In *rhomboid transposition rotational flap*, a full-thickness (extending down to presacral fascia) rhomboid-shaped flap is raised which is then rotated into the defect. *Limberg* modified this approach by lateralizing the distal portion of the suture line to prevent suture line breakdown [216].

Karydakis described the "advancement" flap; the skin, abscess, and sinus were widely excised by an elliptical asymmetrical, then the skin edge closest to the midline was mobilized to create a flap, which was secured deep at the underlying sacrococcygeal fascia and superficially at the other skin edge, thus flattening the natal cleft and avoidance of midline incisions [193].

A meta-analysis analyzed the effect of primary closure vs rhomboid excision and Limberg flap [214]. Limberg flap was found to be significantly superior to primary closure for wound dehiscence (0.9%, Limberg flap group, vs 6.5%, primary closure group; p = 0.05), but there was no difference seen in terms of disease recurrence (0.79%, Limberg flap group, vs 8.4%, primary repair group; p = 0.073).

Karydakis reported a recurrence rate of 1% in a cohort of 7471 patients, out of whom 95% were followed up for 2–20 years [217]. A systematic review of the Karydakis procedure showed a reported recurrence rate of 3.9% [213].

A meta-analysis (6 RCTs, n = 951) compared midline primary closure with off-midline primary closure or flap techniques [206]. It showed that recurrence rate was significantly higher after midline closure compared with off-midline closure (RR 2.32, 95% CI 0.98–5.45; P = 0.023). The same meta-analysis also compared off-midline primary closure techniques: advancement flaps vs rotational flaps [206]. No significant difference was seen between either group (Karydakis flaps or Bascom cleft lip flap vs Limberg) in terms of disease recurrence, superficial skin infection,

or wound dehiscence rates. A recent meta-analysis (8 RCTs, $n = 1121$) found comparable recurrence rate between Limberg and Karydakis flap [218]. Another big meta-analysis suggested lower recurrence rates with the Karydakis flap (1.9%) as compared to Limberg flap (5.2%) on long-term follow-up [219].

4.4.6 Minimally Invasive Surgical Techniques

In endoscopic pilonidal sinus treatment (EPSiT), the fistuloscope is inserted into an enlarged pit (0.5 cm) to directly visualize all sinus tracts. All hairs and debris are removed, and the cavity is ablated using monopolar electrocautery under direct vision, with or without the injection of a sclerosant [220]. This procedure can be performed under local anesthetic and has been associated with reduced pain and hospital stay, faster healing, and earlier return to work. In addition, EPSiT supposedly offers more accurate identification of all sinus cavities and lateral tracts via direct visualization. Complications of this procedure include superficial skin infection, hematoma, persistent discharge, and weighted mean recurrence rate of around 6–8% across several studies [221]. A systematic review of EPSiT (9 studies, 497 patients) showed recurrence rate of 4.02% with a median follow-up of 12 months (range 2.5–25 months) [222].

However, there is a strong criticism of EPSiT procedure [223]. LOCULA (laying open and curettage under local anesthesia) is a logistically smaller and technically easier procedure than EPSiT with comparable or rather better success rates (healing rate of 96–97% in LOCULA vs 92–96% in EPSiT) [199, 205, 207, 221, 223]. LOCULA involves deroofing, whereas endoscopic treatment entails just widening of sinus openings. Undoubtedly, deroofing leads to proper and thorough debridement of the hairs and infected lining of the pilonidal sinus cavity than is possible with an endoscope. Deroofing also leads to better drainage and easier and better cleaning of the cavity in the postoperative period [199, 205, 207, 221, 223]. Therefore, deroofing is preferred over simple incision in any abscess or localized sepsis. Thus, LOCULA has several advantages over endoscopic treatment [223]. Moreover, the use of endoscopic treatment is logical and justified in deeper places like the abdominal cavity where access otherwise would entail a large incision. However, the use of expensive endoscopic equipment in a subcutaneous pathology is difficult to justify.

4.4.7 Importance of Long-Term Follow-Up and Recurrence Rates

A comprehensive study of over 80,000 patients studied over the past 180 years on recurrence rates following various surgical treatments of pilonidal sinus disease was recently published [219]. This study emphasized the importance of studying

recurrence rates as a function of follow-up times. It was demonstrated that quoting recurrence rate in the absence of comparable follow-up durations may bias recurrence figures by a factor of 20. Therefore, it was recommended that long-term follow-up (preferably minimum of 5–10 years) must be stated if reliable conclusions about recurrence rates of any procedure have to be relied upon.

4.4.8 Conclusions

A conservative approach may be suitable for those patients with asymptomatic pits. After analyzing all the evidence, LOCULA should be the frontline treatment for acute pilonidal abscess, chronic pilonidal sinus, and complicated pilonidal sinus. It should be preferred over excisional procedures (midline closure or flap procedures or leaving open with healing by secondary intention). Evidence clearly points that excision is unnecessary and leads to overdoing in pilonidal disease [199, 205, 223, 224]. Pilonidal sinus (including acute abscess) is very much similar to any subcutaneous abscess and should be treated like one [199]. Logically also, excision is unwarranted as pilonidal disease is not a malignancy [199]. Standard treatment of a routine abscess, simply laying open and curettage of abscess cavity, should suffice as adequate treatment for pilonidal sinus. LOCULA is also much less morbid (can be done under local anesthesia, no admission required, resumption of normal work within hours, and much smaller wound), technically simple, economical, and safe, doesn't alter the normal anatomy, and can be easily done in case of a recurrence. Its long-term cure rates (95.5–97%) are comparable, rather better than all other available procedures [199, 205, 223, 225].

The advantage attributed to different flap procedures is that they flatten the contour of the buttock cleft and thus help to prevent long-term recurrence [226, 227]. However, these procedures alter the anatomy permanently which may not be preferred by many patients. A recent study evaluating the preference of patients regarding the procedure for pilonidal sinus showed that 97.1% (33/34) patients preferred buttock contour-preserving procedures and only 2.9% (1/34) said that they would prefer buttock contour-flattening surgery (flap procedures) [194, 195]. The reasons given by the patients for not preferring buttock contour-flattening surgery were permanent alteration of normal body anatomy (loss of buttock's contour), poor cosmesis due to flattening of the contour of the buttocks, and bigger scar. Periodic cleaning of back hairs required in contour-preserving procedures, though cumbersome, was preferred over the disadvantages of buttock contour-flattening surgery [194, 195].

In cases where the laying open and curettage procedure fails repeatedly, a flap procedure should be attempted. Amidst this scenario, the place of endoscopic procedure like EPSiT will be decided only after long-term results of this procedure are available.

Editorial Comment

Compliments to Dr. Garg for the excellent review on a subject often not properly managed. I observed that he has not mentioned anal dilatation in the management of fissure-in-ano. The procedure is nearly 200 years old and was popularized by the legendary Goligher.[1] For decades it remained a useful way of managing patients of fissure. We have practiced anal dilatation throughout our careers with satisfying results. It is a simple procedure. All it needs is adequate relaxation of the anal sphincters that can be achieved with spinal or caudal anesthesia. First, a digital examination is gently done to evaluate the extent of the fissure, followed by inspection through a small anoscope. This is followed by gentle dilatation done initially with one finger. Once adequately dilated it is repeated by more fingers. No forceful dilatation is done to minimize sphincter damage which may cause post-procedure anal incontinence. Almost all such incontinence is temporary. We have not encountered even one instance of permanent incontinence. However, all patients are informed of the possibility of incontinency before the procedure. The reported incontinence rate noted in one study was 3.8%.[2] We are aware that fear of incontinence is a concern, but we believe that if one can avoid too much stretching for sphincter dilatation, this problem may not be as serious as has been suggested.

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Chapter 5
Progressive Familial Intrahepatic Cholestasis

Rajeev Khanna and Vipul Gautam

Case Vignettes

Case 1: A 12-year-old boy presented with refractory pruritus since late infancy, mild jaundice, severe growth failure, short stature, and intermittent small bowel type of diarrhea not requiring any rehydration therapy. His pruritus was severe excoriating, interfering with his daily life, play, and schooling. He had an external biliary diversion surgery at the age of 6 years with temporary relief in pruritus for a year, but a decrease in fistula output was soon followed by recurrence of pruritus. On examination, he had coarse, scaly skin, hepatomegaly, and splenomegaly (liver 5 cm and spleen 3 cm below the costal margins). There were small esophageal varices on endoscopy. He was taken up for living-donor liver transplantation. Post-transplant, his pruritus resolved, but his diarrhea worsened with development of steatosis in the graft within 6 months. Exome sequencing revealed homozygous mutation in ATP8B1 gene (c.589_592delinsCTCCA) suggestive of progressive familial intrahepatic cholestasis (PFIC) type 1.

Case 2: A 3-month-old infant presented with persistent conjugated jaundice since 1 month of life with pigmented stools. Subsequently he developed pruritus by 6 months of age. His jaundice persisted with progressive portal hypertension and decompensation by 2 years of age. Over this period, he suffered multiple episodes of variceal bleeding which were managed with endotherapy. He underwent a successful living-donor liver transplantation at the age of 27 months. The explant liver showed deficient bile salt export pump (BSEP) on immunostaining suggestive of PFIC2.

Case 3: A 19-year-old adolescent presented with four episodes of recurrent jaundice and pruritus since the age of 10 years. Each episode was associated with dark urine and pale stools, and was preceded by fever and upper respiratory illness, and jaundice and pruritus lasted for 1–2 months. There was no prodrome to suggest viral

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hepatitis, painful abdomen, or decompensation in the form of ascites or hepatic encephalopathy. There was history of gallstone in elder brother aged 20 years. On examination, there were deep jaundice, scratch marks, hyperpigmentation, and mild hepatomegaly (liver 3 cm below the costal margin). Liver function tests (LFT) showed bilirubin 30.4 (direct 17.8) mg/dl, AST (aspartate aminotransferase)/ALT (alanine aminotransferase) 54/40 i.u. /L, ALP (alkaline phosphatase)/GGT (gamma-glutamyl transpeptidase) 325/22 i.u. /L. Fibroscan was 8.8 kPa, and liver biopsy showed preserved acinar architecture with prominent canalicular cholestasis and absence of fibrosis. He was started on ursodeoxycholic acid (UDCA), cholestyramine, and hydroxyzine. Jaundice and pruritus gradually resolved and he was continued on UDCA.

Case 4: Two sisters (14-year and 4-year-old) presented with pruritus. They were being followed up by a dermatologist. Incidentally, they were found to have elevated liver enzymes and referred to a pediatric hepatology unit. On evaluation, both had growth failure and mild liver disease (normal bilirubin, mild elevation of transaminases, low GGT <50 i.u./L, fibroscan 5.6 kPa and 6.5 kPa, and pruritus refractory to UDCA, cholestyramine, and rifampicin. Liver biopsies showed mild bland cholestasis with absence of fibrosis. Both were taken up for internal biliary diversion (cholecystojejunocolostomy) followed by improvement in pruritus. Their liver disease remained stable over the next 7 years.

Case 5: A 12-month-old infant presented with jaundice since 9 months of age and abdominal distention for 1 month. On examination, he was icteric with hepatosplenomegaly. His investigations showed bilirubin 12.6 mg/dl, AST/ALT 263/94 IU/L, ALP/GGT 856/28 IU/L, international normalized ratio (INR) 1.45, and fibroscan 45 kPa. Ultrasound showed cirrhotic liver with presence of multiple heteroechoic mass lesions in segments 2, 4a, 5, and 6. Fine needle aspiration cytology showed trabecular variety of hepatocellular carcinoma (HCC) with Edmondson-Steiner stage III. Liver biopsy from the non-lesional site showed marked acinar disarray, canalicular cholestasis, feathery degeneration, giant cell transformation, and advance fibrosis; there was deficient BSEP protein on immunostaining. The child died before the family decided about liver transplantation.

Case Scenario 6: Two boys (8.5-year and 10-year-old) born out of a consanguineous union presented with pruritus and intermittent low-grade jaundice. Both had severe growth failure, clubbing, fat-soluble vitamin deficiencies, and shrunken liver; older one had massive splenomegaly (9 cm below the costal margin) and varices on endoscopy. There was history of antenatal pruritus (intrahepatic cholestasis of pregnancy) during all six pregnancies in mother. LFT showed mild conjugated jaundice, elevated AST/ALT (143/147 and 122/69 i.u./L), and ALP/GGT (474/225 and 396/112 i.u./L). Liver biopsies showed cirrhosis with features of cholestasis. Immunostaining showed deficient multidrug resistance protein-3 (MDR3) suggestive of PFIC3. Both underwent liver transplantation (living related in the younger and deceased donor in the older) within 6 months and 1 year of presentation. The diagnosis was later confirmed on exome sequencing—homozygous mutation in ABCB4 gene (c.3393C > A).

5.1 Introduction

The abovementioned case vignettes represent varied hepatic manifestations of related genetic disorders collectively termed as progressive familial intrahepatic cholestasis (PFIC). PFICs are a heterogenous group of autosomal recessive disorders of biliary transporters with varied spectrum of hepatic manifestations ranging from mild liver disease, isolated pruritus affecting quality of life, recurrent cholestasis, gallstones, and intrahepatic cholestasis of pregnancy to neonatal cholestasis, infantile liver failure, portal hypertension, growth failure, and advance end-stage liver disease necessitating liver transplantation (LT) [1–3]. The first three of these disorders (types 1, 2, and 3) have been numbered based on their discovery. The estimated prevalence in the western world is around 1:18000 with PFIC comprising 9–13% of diagnosis among children with intrahepatic cholestasis or liver disease. Overall, PFIC2 (BSEP deficiency) is the commonest (21–91%) followed by PFIC1 (FIC1 deficiency) (30–41%) [4–8]. With advancement in genetic technology, newer entities like mutations in tight junction protein-2 (TJP2), farnesoid-X receptor (FXR), and myosin-5B (MYO5B) have come into picture [1, 9–11]. Hence, the better terminology for each one of them is by the name of the defective transport or structural protein or the gene involved. The current text discusses the pathophysiological basis, clinical characterization, diagnosis, histological features, and management strategies for these disorders. Table 5.1 presents the differentiating features of different types of PFIC, their clinical course, and outcome.

5.2 Biliary Transport and Regulation

Bile constitutes bile acids, phospholipids, conjugated bilirubin, cholesterol, heavy metals, and several different detoxified and modified metabolites. Bile acids are the main components of bile, and it is the flux/recirculation of bile acids that is the main driving force to bile formation. Hepatocyte polarity is primarily responsible for the synthesis and transport of bile acids. Bile acids are synthesized in hepatocytes either via neutral (classical) pathway or acidic (alternative) pathway. These bile acids are then conjugated to either glycine or taurine and become bile salts which are negatively charged at physiological pH. The basolateral hepatocyte membrane (sinusoidal membrane) is responsible for the uptake of conjugated bile salts via sodium-dependent bile salt transporter (NTCP, gene *SLC10A1*). The multispecific organic anion transporting polypeptides like OATP-A and OATP-C and to some extent OATP8 are involved in sodium-independent bile salt uptake. Bile acids in the form of bile salts are then excreted out of the hepatocyte through canalicular membrane via bile salt export pump (BSEP), an ATP-binding cassette (ABC) transporter which is encoded by ABCB11. Hepatocyte excretion of phospholipids is mediated by multidrug resistance protein-3 (MDR3) encoded by ABCB4 gene [17, 18]. This protein (MDR3) acts as a floppase, which translocates phospholipids from the inner

Table 5.1 Different types of PFICs—genetic defects, transporters, and clinical course (based on References [1–9, 11–16])

Mutated protein (disease)	FIC1 deficiency (PFIC1)	BSEP deficiency (PFIC2)	MDR3 deficiency (PFIC3)	TJP2 mutations	NR1H4 (FXR) mutations	MYO5B mutations
Gene	ATP8B1	ABCB11	ABCB4	TJP2	NR1H4	MYO5B
Gene location	18q21–22	2q24	7q21	9q21.11	12q23.1	18q21.1
Function	Translocation of aminophospholipids from outer to inner leaflet of lipid bilayer (flippase)	Bile salt export	Translocation of phosphatidylcholine from inner to outer leaflet of lipid bilayer (floppase)	Intracellular anchoring leading to sealing of canaliculi	Expression of biliary transporters like BSEP and MDR3	Intracellular trafficking and localization of apical membrane transporters
GGT	Normal	Normal	High	Normal	Normal	Normal
Elevation of transaminases	Mild	Moderate to severe	Mild to moderate	Moderate	Moderate	Mild
Gallstones	–	++	+++	–	–	–
Recurrence cholestasis	+ (BRIC1)	+ (BRIC2)	++	–	+	–
Liver failure	–	++	–	++	Early (as infantile liver failure)	–
Extrahepatic features	++ (diarrhea, pancreatitis, deafness, respiratory distress)	–	–	+ (respiratory, neurological)	–	Diarrhea (as part of MVID)
HCC	–	+++	+	++	–	–
Histology	Bland canalicular cholestasis, coarse granular canalicular bile on EM	Giant cell transformation, duct loss	Bile ductular proliferation, cholangiolytic changes	Bland cholestasis	Intralobular cholestasis, ductular reaction, giant cell transformation	Giant cell transformation, hepatocellular and canalicular cholestasis
Biliary bile acids	Low	Very low	Normal	–	–	–

Biliary phospholipids	Normal	Normal	Low	–	–	–
Progression to ESLD	Slow	Rapid	Progression variable	Rapid	Very rapid	Slow
Natural history	Growth failure, severe pruritus	Growth failure, pruritus, HCC, ESLD requiring LT in early childhood	PHTN, growth failure, cholestasis, gallstones, ESLD by end of first or second decade	Similar but rapid course than PFIC2, increased HCC risk	Requires LT in infancy	Associated MVID may need multi-visceral transplant
Unique features	Post-transplant diarrhea and graft steatosis	Risk of recurrence post-LT due to Allo-antibody against BSEP	Association with ICP, drug-induced cholestasis, CIC, LPAC	–	Post-LT steatosis	Isolated liver disease may be protective against MVID

Abbreviations: *BRIC* benign recurrent intrahepatic cholestasis, *BSEP* bile salt export pump, *CIC* contraceptive-induced cholestasis, *ESLD* end-stage liver disease, *FIC1* familial intrahepatic cholestasis type 1, *FXR* farnesoid-X receptor, *GGT* gamma-glutamyl transpeptidase, *HCC* hepatocellular carcinoma, *ICP* intrahepatic cholestasis of pregnancy, *LPAC* low phospholipid-associated cholestasis, *LT* liver transplantation, *MDR3* multidrug resistance protein-3, *MVID* microvillus inclusion disease, *MYO5B* myosin-5 B, *NR1H4* nuclear receptor subfamily 1 group H member 4, *PFIC* progressive familial intrahepatic cholestasis, *TJP2* tight junction protein 2

to the outer leaflet of the lipid bilayer of the canalicular membrane. Familial intrahepatic cholestasis 1 (FIC1) protein, encoded by ATP8B1 gene, is also expressed on canalicular membrane, and it helps in bile salt transport by maintaining the enrichment of aminophospholipids on the inner leaflet of the canalicular membrane (flippase). In most eukaryotic cells, phosphatidylcholine and sphingolipids are concentrated in the exoplasmic leaflet, whereas the aminophospholipids (phosphatidylserine and phosphatidylethanolamine) are largely confined to the cytoplasmic leaflet. FIC1 protein thus helps in maintaining this asymmetrical gradient (Fig. 5.1) [19].

Expression of ABCB11 and ABCB4 and other transporters is regulated by farnesoid-X receptor (FXR) protein, which is a nuclear receptor and transcription factor and a natural ligand for bile acids. FXR binds as a heterodimer with the retinoid X receptor (RXR) which then exerts its actions. FXR can also downregulate the transcription of specific target genes indirectly via another nuclear receptor, the small heterodimer partner (SHP). FXR plays an important role in bile acid homeostasis. With high hepatic bile acid levels, FXR represses bile acid synthesis and uptake, and increases their export out of the hepatocytes. In the mucosa cells of the ileum, bile acids bind to FXR leading to activation of the transcription of fibroblast growth factor (FGF19), and subsequently FGF19 is secreted into the portal circulation. At

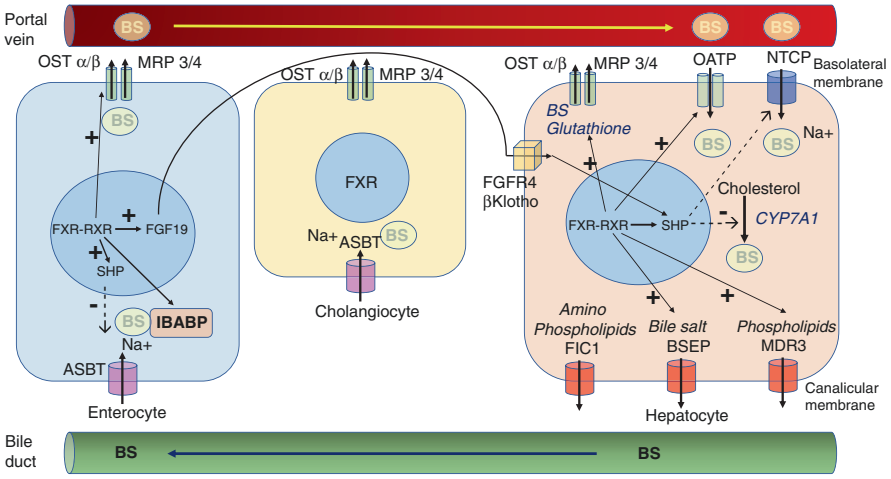


Fig. 5.1 Biliary transport and role of FXR. Diagram showing biliary transporters in the hepatocytes, cholangiocytes, and enterocytes and the central role of farnesoid-X receptor in regulating bile acid synthesis and transport via FGF19 and SHP proteins [17, 19, 20]. Abbreviations: *ASBT* apical sodium bile acid transporter, *BS* bile salt, *BSEP* bile salt export pump, *CYP* cytochrome P enzyme, *FIC1* familial intrahepatic cholestasis type 1, *FXR* farnesoid-X receptor, *FGF19* fibroblast growth factor 19, *FGFR4* fibroblast growth factor receptor 4, *IBABP* intestinal bile acid-binding protein, *MDR* multidrug resistance protein, *MRP* multidrug resistance-associated protein, *Na* + sodium ion, *NTCP* sodium taurocholate cotransporting polypeptide, *OATP* organic anion transporting polypeptide, *OST* organic solute transporters, *RXR* retinoid X receptor

the hepatocyte surface, FGF19 binds to FGFR4/bKlotho leading to activation of transcription of short heterodimer partner (SHP). This complex interaction of FGFR4/bKlotho and FXR-SHP blocks bile acid synthesis by blocking the transcription of CYP7A1 enzyme which is mediated by liver receptor homologue-1 (LRH-1) and hepatocyte nuclear factor-4α (HNF4α). CYP7A1 is the rate-limiting enzyme in the synthesis of bile acids from cholesterol. The FXR-RXR complex directly induces the expression of organic solute transporters (OST) α and β (in ileal enterocytes and in the basolateral membrane of hepatocytes) as well as intestinal expression of the intestinal bile acid-binding protein (IBABP). In addition to directly activating the main BS efflux systems, under cholestatic conditions, FXR concurrently downregulates the main BS uptake systems, primarily NTCP in the basolateral membrane of hepatocytes and apical sodium-dependent bile acid transporter (ASBT, gene *SLC10A2*) in the ileal epithelium (Fig. 5.1) [19, 20].

Intracellular trafficking of the transporters including BSEP and localization to the canalicular membrane is regulated by myosin-5B (MYO5B)/RAB11A recycling endosome pathway [1, 10]. Finally, there are tight junction proteins (TJPs 1, 2, 3) which are cytoplasmic proteins and not part of tight junction itself, but closely associated with other proteins called claudins, which form tight junctions (Fig. 5.2) [1, 21].

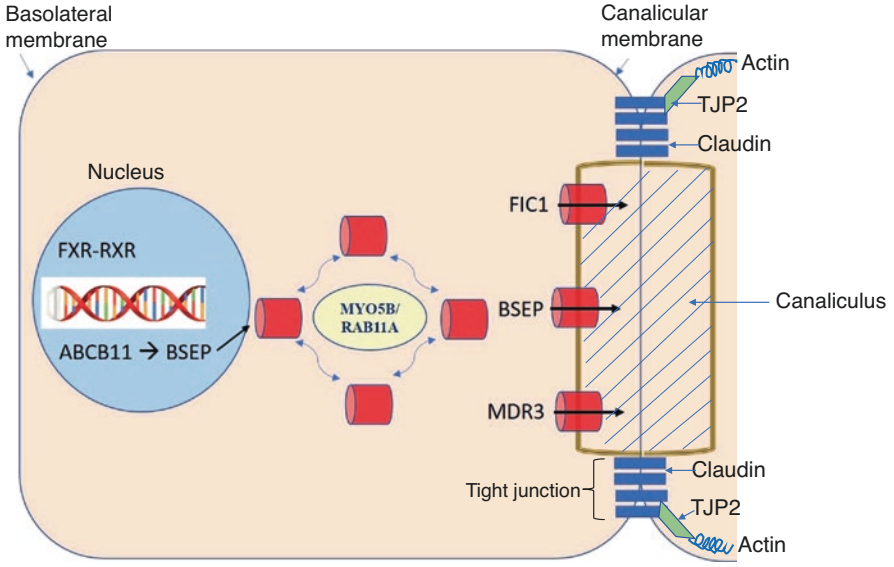


Fig. 5.2 Biliary transporters in PFIC. Diagram showing various biliary transporters involved in PFICs. Farnesoid-X receptor mediates the expression of transporters like BSEP which then are trafficked via myosin-5B and RAB11A recycling endosome pathway to the plasma membrane [9, 10, 17, 20]. Abbreviations: *BSEP* bile salt export pump, *FIC1* familial intrahepatic cholestasis type 1 protein, *FXR* farnesoid-X receptor, *MDR3* multidrug resistance protein-3, *MYO5B* myosin-5B protein, *RXR* retinoid X receptor, *TJP2* tight junction protein 2

5.2.1 Mechanism of Pruritus in PFIC

As pruritus is the dominant manifestations of most PFICs, it is important to understand its pathogenesis. Mechano-insensitive C nociceptors in the skin with unmyelinated nerve endings are sensitive to itching. These C fibers play a role in transmitting the signals from the skin to dorsal route ganglion from where it goes to ventromedial nucleus of thalamus via spinothalamic tract. From the thalamus itch signals reach to the primary sensory cortex, inferior parietal lobe, and anterior cingulate gyrus. Both pain and itch fibers involve the activity of TRPV1 (capsaicin receptor). TRPV1 is directly activated by capsaicin (red hot chili pepper), high temperature (>43 °C), low pH (<5.9), and lysophosphatidic acid (LPA). LPA is an important mediator of cholestatic itch. Autotaxin is an enzyme which converts lysophosphatidylcholine into LPA and is a useful marker of cholestasis and pruritus. Neurotransmitters involved in the transmission of itch sensation are natriuretic polypeptide b (Nppb) and gastrin-releasing peptide (GRP). Various pruritogens involved in the pathogenesis are histamine, bile salts, serotonin, LPA, endogenous opioids, progesterone, and estrogen, and have implication in specific targeted therapies against pruritus [22].

5.3 FIC1 Deficiency (Byler's Disease, PFIC1)

FIC1 protein is a member of the P4 family of P-type ATPases, ATP-dependent membrane transporters known as phospholipid "flippases." FIC1 is expressed in a variety of tissues, including the liver, intestine, pancreas, and kidneys [23]. When FIC1 is not available to help maintain normal distribution of lipids between the two membranes of the lipid bilayer, the canalicular membrane may become vulnerable to bile canaliculus. Proteins in this membrane, including BSEP, also may have impaired function contributing to cholestasis. It has been proposed that FIC1 also plays a role in membrane trafficking and vesicular transport. FIC1 may also play a role in the innate immune response, attenuating the inflammatory response, perhaps through a role in endocytosis [24, 25].

5.3.1 Genotype-Phenotype Correlation

Genotype-phenotype associations are complex with ATP8B1 mutations. The disease may represent a continuum of severity, with PFIC typically diagnosed in patients with likely complete loss of FIC1 function due to nonsense, frameshift, and large deletion mutations. Patients with milder phenotypes, including episodic cholestasis like benign recurrent intrahepatic cholestasis 1 (BRIC1), transient neonatal cholestasis, and intrahepatic cholestasis of pregnancy 1 (ICP1), are taken as

continuum of FIC1 deficiency, and the protein function is only partially impaired in them mostly related to missense mutations. In approximately 10% patients with PFIC1, only one mutated allele or no mutation is seen. In these patients, possible disease mechanisms include either the presence of mutations in regulatory sequences of the gene or in the other genes involved in the transcription or protein trafficking of FIC1 protein [1, 6–8, 26, 27].

5.3.2 Clinical Profile

A typical child with FIC1 disease presents with jaundice within the first few months of life. This is followed by diarrhea and growth failure. Pruritus is the dominant feature and is usually out of proportion to jaundice; it usually develops after 6 months of age after the neural pathways for concerted scratching are well developed. Biochemically, patients have conjugated hyperbilirubinemia, normal serum gamma-glutamyl transpeptidase (GGT), high serum bile acids, and mildly elevated transaminases. In view of wider tissue distribution of FIC1, patients often have extrahepatic manifestations during the course of disease, such as diarrhea, pneumonia, hearing loss, pancreatic disease, resistance to parathyroid hormone, growth impairment beyond that attributable to cholestasis, and delayed puberty and sexual development [1, 4, 6, 8, 18].

5.3.3 Histology

Histology reveals bland intracanalicular cholestasis without signs of significant hepatocyte injury. With disease progression, inflammation, fibrosis, bile duct proliferation, and cirrhosis develop. Transmission electron microscopy may demonstrate coarsely granular bile in the canaliculus. Liver biopsy usually shows normal histology or hepatocellular cholestasis and cholate injury, mostly centrilobular. Immunostaining for FIC1 has not been established for routine clinical use. However, there are surrogate markers of FIC1 deficiency like reduced canalicular staining for GGT, CD10, and carcinoembryonic antigen [1, 28].

5.3.4 Benign Recurrent Intrahepatic Cholestasis (BRIC)

Recurrent attacks of cholestasis, termed as BRIC, present as attacks of jaundice and pruritus separated by symptom-free intervals. These episodes may start at any age (1–50 years, usually before 20 years) and are associated with fatigue, malaise, anorexia, steatorrhea, dark-colored urine, and weight loss. There is no progression to cirrhosis or long-term complications of chronic liver disease. Attacks usually are

preceded by a minor illness and consist of a preicteric phase of 2–4 weeks (characterized by malaise, anorexia, and pruritus) and an icteric phase that may last from 1 to 18 months. In some patients, hormonal factors such as the use of oral contraceptives or pregnancy or antibiotics may be associated with precipitation of an attack. During the icteric phase, the concentrations of serum bile acid, bilirubin, and alkaline phosphatase are increased with low GGT; however, in the intervening periods, biochemistry is completely normal [1, 3].

5.3.5 Disease Course and Outcome

Early in the course of the disease when pruritus remains the chief and devastating symptom affecting the quality of life, partial external biliary diversion (PEBD) or internal biliary diversion (PIBD) is helpful. With the advancement of liver disease, eventually these children may require liver transplantation [4, 6, 8].

5.4 BSEP Deficiency (PFIC2)

Severe BSEP deficiency is the commonest form of PFIC worldwide [5–8, 29]. With defective or deficient BSEP, there is accumulation of bile acids within the hepatocyte with accompanying toxic damage and progression of disease.

5.4.1 Genotype-Phenotype Correlation

Although earlier reports did not suggest genotype-phenotype correlation, this has been proved recently [8]. Severe phenotypes are often associated with mutations leading to premature protein truncation or failure of protein production. Milder phenotypes with reduced transport capacity of BSEP may be caused by mutations in one or both copies of this gene. True pathogenic mutation may be present on only one allele, although polymorphisms (such as p.V444A) may influence the levels of protein expression or function on the other allele, and this means that such individuals have reduced function on both alleles. Thus, there may be reduced or absent function and defective translocation. It has been suggested that around 25% of ideal BSEP function is the threshold for patients at risk of cholestasis, but this may be influenced by drugs, pregnancy, viruses, malignancy, or other less recognized precipitants [1, 6, 30]. Variants of ABCB11 have also been associated with BRIC2 drug-induced cholestasis and some cases of ICP, and these variants are milder, missense type and located in less conserved regions of the gene [1].

Two mutations, relatively common (58%) among European patients with BSEP deficiency (p.E297G or p.D482G), lead to some residual function in up to 45%.

Patients with at least one copy of either of these mutations can present with complete PFIC2 phenotype or a less severe phenotype. They also have been shown to have better outcomes, and improved responses to some treatments, compared with other patients with early-onset BSEP deficiency [6]. From the European cohort of BSEP, it was found that portal hypertension was more frequent and survival with native liver poor in those without D482G mutation in contrast to those with that mutation. Hence, D482G represents a more insidious and milder form of BSEP [31].

5.4.2 Genetic Classification of BSEP

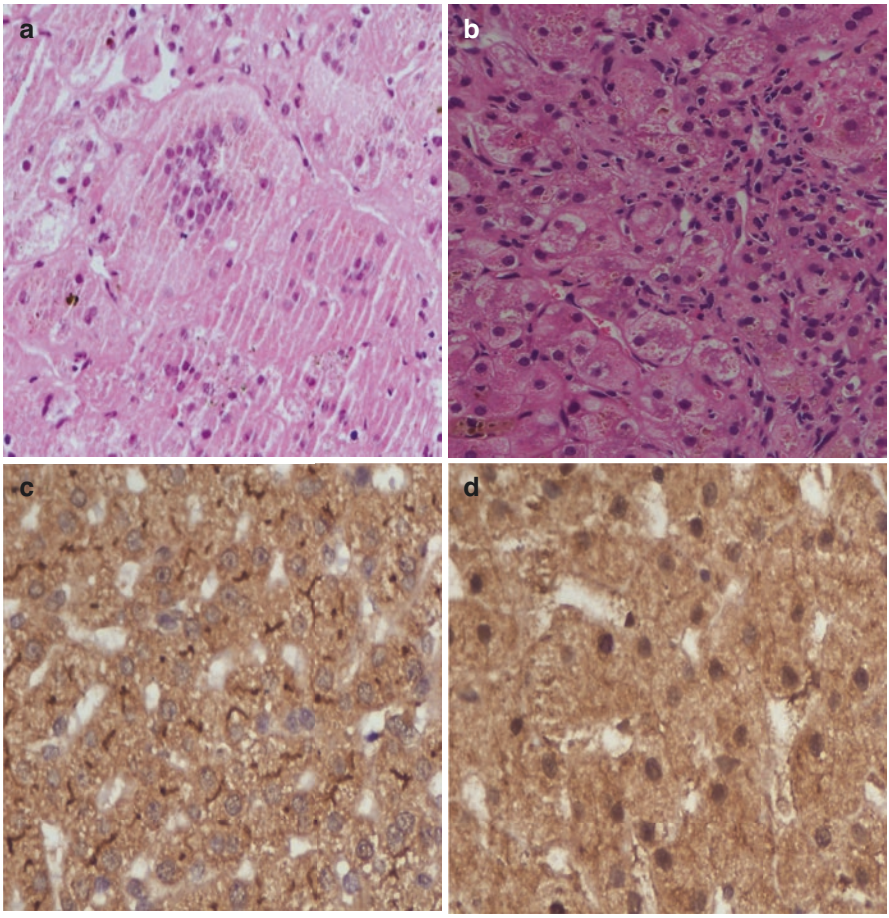
The results of multicentre NAtural course and Prognosis of PFIC and Effect of biliary Diversion (NAPPED) consortium comprising a cohort of 264 children with homozygous or compound heterozygous pathological ABCB11 mutations categorized BSEP patients on the basis of type of mutations: (i) *BSEP1*, those with at least one copy of p.D482G or p.E297G (mildest phenotype with least severe disease); (ii) *BSEP2*, those with at least one missense mutation (yet not p.D482G or p.E297G); and (iii) *BSEP3*, those with mutations causing completely nonfunctional protein or total absence of BSEP expression on immunostaining. It was found that BSEP1 patients had better long-term outcomes with their native livers than BSEP2 and BSEP3 (20.4 versus 7.0 versus 3.5 years, respectively). This classification also has implication to decide management strategy for these patients as biliary diversion surgery was beneficial for BSEP1 and 2 patients, but not for patients with BSEP3 [32].

5.4.3 Clinical Profile

Children with significant reduction in BSEP function generally present in the first few months of life, and manifest as neonatal or infantile cholestasis, growth failure, fat-soluble vitamin deficiencies, pruritus, high serum bile acids, and moderate to severe elevation of transaminases and normal GGT. Spectrum, however, varies from mild intermittent cholestasis (BRIC2), isolated pruritus to rapidly progressive liver disease necessitating LT by the first few years of life [4–8].

5.4.4 Histology

Liver histology shows marked intracellular cholestasis, usually obvious giant cell transformation [28]. A proportion of patients also show destructive bile duct damage leading to duct loss [29]. BSEP antibody staining is abnormal or absent in more than 90% of severe cases [1] (Picture 5.1).



Picture 5.1 Histological features in children with PFIC. Panel A shows liver biopsy of a 4-month-old boy with PFIC2 with evidence of giant cell hepatitis in (400X, Hematoxylin and Eosin, H&E stain). Panel B shows liver biopsy of a 9-month-old boy with PFIC2 with evidence of hepatocellular and canalicular cholestasis, feathery degeneration, and periportal inflammation (400X, H&E stain). Panel D shows liver biopsy of a 10-year-old boy with PFIC3 with features of cholestasis, growth failure, pruritus, and portal hypertension showing absent MDR3 on immunostaining in comparison with the control liver biopsy of a child with hepatitis B (Panel C) (400X, MDR3 Immunostain)

5.4.5 Disease Course and Outcome

Several drugs like ursodeoxycholic acid (UDCA) and various other molecular chaperones have been tried for BSEP deficiency. However, the disease typically progresses to end-stage liver disease by the first few years of life [4]. Diversion surgery is helpful before the development of advanced fibrosis (Metavir stage <F3). PEBD relies on the presence of bile acids in the bile and has shown a better response in those shown to have some residual BSEP function. Good response to PEBD is seen in up to 76% of individuals with at least one copy of either of the variants p.E297G

or p.D482G [12]. Many patients eventually require LT for debilitating pruritus affecting their quality of life, and before the development of end-stage liver disease [4, 6, 8, 12]. Despite early transplant, up to 15% of these children develop hepatocellular carcinoma, either clinically or at explant, and mostly under 5 years of age [33]. Due to selective expression of BSEP only in the liver, unlike FIC1 protein, transplantation is the definite cure for the disease [1].

5.5 MDR3 Deficiency (PFIC3)

MDR3 deficiency or PFIC3, encoded by ABCB4 gene, is a type of cholangiopathy—biliary injury caused by elevated biliary bile acids [34]. Estimated incidence rate is 1:50,000–1:1,00,000. The protein transports phospholipid (chiefly phosphatidylcholine) from the inner to the outer leaflet of the canalicular membrane (flippase), which is then available for incorporation into bile micelles. Due to the deficiency of phospholipids in the bile, there are non-micellar free bile acids. These free bile acids have detergent action and cause injury to the cholangiocyte membranes ("toxic bile concept"). Hence, there is no retention of bile acids in the hepatocytes. Moreover, as biliary cholesterol solubilization also depends on appropriate concentration of bile acids and phospholipids, this mismatch also contributes to formation of extra- and intrahepatic crystals and gallstones [35].

5.5.1 Genotype-Phenotype Correlation

Various mutations in the ABCB4 gene have been recognized and characterized as non-sense mutations and frameshift deletions leading to complete absence of protein (I), missense leading to defective maturation of protein (II), activity (III), stability (IV), and variants without detectable effects. Heterozygotes for complete loss of function alleles have 50% function of the protein, which is sufficient to cause damage in some individuals [36]. Such individuals may be found to have some evidence of liver disease on evaluation in the first few decades but may remain asymptomatic, and later on present with end-stage liver disease in adulthood, or with hepatobiliary malignancy. Thus, heterozygous relatives of patients with MDR3 deficiency are therefore at increased risk of slowly progressive disease and should not be considered as suitable donors without proper screening [1].

5.5.2 Clinical Profile

In the typical form of PFIC3 presentation, the disease presents as childhood cholestasis (median age 4.7 years), some patients present in infancy as conjugated hyperbilirubinemia. Symptoms include pruritus, hepatosplenomegaly, jaundice, and features of portal hypertension. Rapid progression to liver cirrhosis and

decompensation happens at an age between 3 and 15 years—half require LT around the end of first decade [4]. Even complete deficiency of MDR3 can take several years before presenting clinically, and hence some patients may present late in adolescence or adult life with mild to moderate jaundice, gallstones, or hepatolithiasis. Transaminases are moderately elevated, but alkaline phosphatase and GGT are markedly high [13, 14, 36]. ABCB4 mutations also predispose adult patients to gallbladder carcinoma and cholangiocarcinoma [36].

5.5.3 Histology

Liver biopsy shows cholangiolytic changes—bile ductular proliferation, hepatocellular and canalicular cholestasis, portal expansion, and fibrosis [28]. In an infant, these histological features may simulate biliary atresia [14]. Immunohistochemical staining for MDR3 may be deficient (missense mutations) or absent (truncated mutations) [36] (Picture 5.1).

5.5.4 Intrahepatic Cholestasis of Pregnancy (ICP)

ICP represents a milder spectrum of MDR3. This is the commonest liver disease during pregnancy and presents typically as pruritus starting at third trimester predominantly affecting hands and feet, with remission of cholestatic features within 2 weeks of delivery. Biochemical abnormalities include elevated fasting bile acid levels, transaminases, alkaline phosphatase, and GGT. Conjugated hyperbilirubinemia is uncommon. This is associated with higher risk of premature delivery, meconium staining of amniotic fluid, respiratory distress, and intrauterine death. Higher serum bile acids are related to increased fetal risk [15]. In a large European cohort of 563 pregnant ladies with ICP, 6 single nucleotide polymorphisms were identified in each of the two genes ABCB4 and ABCB11 showing significant evidence of association. The strongest association signals were seen with rs2109505 in ABCB4 and with rs7577650 in ABCB11 [37]. UDCA is indicated to alleviate pruritus, and early induction of labor is indicated by around 37 weeks. These ladies have increased risk of gallstones later in their lives [15].

5.5.5 Low Phospholipid-Associated Cholelithiasis (LCAP)

LCAP is characterized by an increased risk of early development of gallstones in the gallbladder as well as within the liver (hepatolithiasis). Diagnosis is based on the presence of two of the following: (1) biliary symptoms before the age of 40 years, (2) detection of intrahepatic microlithiasis/sludge by ultrasound (hyperechoic foci),

and (3) recurrence of cholelithiasis after cholecystectomy. Diagnosis is confirmed by microscopic examination of endoscopically sampled hepatic or duodenal bile, which contains aggregated cholesterol crystals or microliths and reduced contents of phospholipids (in relation to bile acids). Sequencing of all exons of ABCB4 may reveal functionally relevant variants. In case of symptomatic gallstones, cholecystectomy with/without bile duct exploration or endoscopic retrograde cholangiography has to be performed. Hepatolithiasis may need localized liver resections for control of recurrent cholangitis [36].

Two less common forms of MDR3 deficiency are drug-induced cholestasis and contraceptive-induced cholestasis (CIC). Drugs especially some antibiotics and psychotropic drugs which inhibit P-glycoproteins can induce cholestatic form of liver injury in the presence of ABCB4 mutations. Similarly, oral contraceptive pills can precipitate cholestasis particularly in those with personal or family history of ICP [13, 36].

5.5.6 Disease Course and Outcome

As there is mismatch in the bile salt and phospholipid pool in MDR3, PEBD is not a suitable option and has not been reported in these children. However, usage of UDCA early in the course of the disease or in milder forms has been shown to halt the progression of disease by its detergent action on the cholangiocyte membrane [14]. But the action is limited due to the inability of UDCA to suppress the synthesis of endogenous bile salts, via FXR [20]. Liver transplantation is the definite treatment for severe MDR3 deficiency presenting as end-stage liver disease [1, 14].

5.6 Natural History and Outcomes of FIC1, BSEP, and MDR3 Deficiencies

The natural history and outcomes of these 3 commonest forms of PFIC have been studied in a recent review with 17 publications describing natural history or epidemiology and 5 publications describing their health-related quality of life (HRQoL). Pruritus was experienced by 11–100% of patients at presentation and by 76–100% of patients at follow-up. Pruritus is often debilitating, associated with abrasions, cutaneous mutilation, hemorrhage, and scarring which corresponds to grade ≥3+ on Whitington scale. Pruritus was identified as the most bothersome symptom in PFIC—more often in types 1 and 2 (76–100%) versus type 3 (25–69%). These children have poor HRQoL as assessed by the Pediatric Quality of Life Inventory (PedsQL) Measurement Model and Infant Dermatitis Scale. The HRQoL scores, physical health, and psychosocial summary scores were poorer in comparison with their healthy peers [4].

PFIC1 children often presented with poor growth (~100%), diarrhea (61%), pancreatitis (8%), and elevated sweat chloride (15%). In PFIC2, there were deficiencies of vitamin D in 3–22% and K in 8% (as bleeds) and cholelithiasis in 28%. There was rapid progression of histological fibrosis in children with PFIC2 in comparison with PFIC1. Among the patients undergoing LT, liver failure and/or HCC was detectable in about 60% of those with PFIC2 but in none of those with PFIC1. Untreated PFIC1 and 2 have mortality rates ranging from 0 to 87% and LT rates 40 to 100%. Reasons for mortality in untreated PFIC are infections, liver failure, bleeding (cerebral, gastrointestinal, splenic), and HCC. The common indications for liver transplantation in children with PFIC are failure of decompensated cirrhosis (78–97%), PEBD (29–67%), severe cholestasis and mutilating pruritus (7–42%), liver failure (32%), growth failure, and development of HCC (10–26%) [4].

5.7 TJP2 Mutations

The tight junction protein-2 (TJP2) or zona occludens 2 is not part of the tight junction between the hepatocytes but is located in the cytoplasm and serves as a link between transmembrane tight junctions and actin cytoskeleton. TJP2 is closely associated with the tight junction proteins called claudins [21]. Deficiency of Claudin-1 has been described, associated with a cholangiopathy termed neonatal ichthyosis-sclerosing cholangitis syndrome [38]. TJP2 is also known as zona occludens 2 (ZO2). Deficiency of TJP2 is associated with cholestasis, but not with cholangiopathy, suggesting that the tight junction barrier function is not badly disrupted. The mechanism of cholestasis is not very clear. The tight junction between the basolateral and canalicular membrane provides a selective barrier since the two membranes differ with respect to protein and lipid composition. Hence, disruption of the TJP2 causes cholestasis by damaging the membrane integrity. Moreover, TJP2 has also been shown to travel to the nucleus, where it is transcriptionally active and inhibits cell cycle progression [21]. Homozygosity for a missense change manifests as hypercholanemia among the Amish population, with reduced penetrance. These patients did not manifest chronic liver disease [39]. On the other hand, biallelic mutations in TJP2 causing complete loss of TJP2 function cause severe progressive liver disease. These patients have very severe liver disease starting from early infancy with cholestasis, elevated bilirubin and transaminases, and normal GGT. Most of these children require LT within the first few years of life. From the description of 12 cases from King's College London, 11 with consanguinity, the median age of presentation was 2 months, and 9 required LT a median age of 4 (1.5–10) years. Due to the extrahepatic distribution of TJP2, respiratory and neurologic symptoms are often seen. Histology shows nonspecific features with intracellular cholestasis and giant cells. Immunohistochemical staining for TJP2 has been useful in identifying cases [9]. Patients with TJP2 deficiency and hepatocellular carcinoma have been described [40].

5.8 NR1H4 (FXR) Mutations

FXR is a bile acid-activated nuclear receptor encoded by NR1H4 (nuclear factor subfamily 1 group H member 4) gene. As explained earlier in the text the central role of FXR in regulating biliary transport, it is easy to understand that FXR mutations with complete loss of its function cause severe cholestasis and liver damage. Four children were reported with homozygous mutations in NR1H4 gene who presented with neonatal cholestasis, liver failure (coagulopathy), low-to-normal GGT, high transaminases, high alpha-fetoprotein levels, and rapid progression to end-stage liver disease. One neonate presented with hydrops (ascites and pleural effusion) with intraventricular hemorrhage at birth. Two infants received LT at the age of 4.4 and 22 months, while other two died at 5 weeks and 8 months, respectively. Liver histology showed intralobular cholestasis with ductular reaction, hepatocellular ballooning, giant cell transformation, and micronodular cirrhosis. There was absence of FXR and BSEP on immunostaining; the latter is attributed to the fact that FXR is required for BSEP expression on the canalicular membrane. Post-LT, one child had mild elevation of transaminases with histological steatosis. This was explained by lack of induction of FGF19 by intestinal FXR which remained deficient after LT [11].

5.9 Myosin-5B (MYO5B) Mutations

Myosin-5B protein plays a role in plasma membrane recycling, transcytosis, and epithelial cell polarization in multiple tissues, chiefly enterocytes, respiratory epithelial cells, and hepatocytes. In the liver, MYO5B interacts with RAB11A to facilitate normal trafficking of ABC transporter proteins, including BSEP, to the canalicular membrane [1]. Autosomal recessive mutations in MYO5B were initially identified in a proportion of patients with microvillus inclusion disease (MVID), a severe form of intractable diarrhea of infancy [10]. A subset of patients with MVID with MYO5B mutations developed cholestasis as well [16]. Recently, mutations in MYO5B have been reported in patients with isolated cholestasis, in the absence of obvious features of MVID [41–43]. The children with MYO5B-related liver disease without MVID present with early childhood cholestasis, pruritus, hepatomegaly, failure to thrive, mild to moderate elevation of transaminases, elevated bile acid levels, and low-normal GGT. Mutations were homozygous and compound heterozygous. Some children show response to UDCA and have transient or recurrent cholestatic features. Around half of the children require some form of biliary diversion (nasobiliary drainage or surgical diversion) [16, 41–43]. A proportion may have resolved MVID [43]. Histology shows hepatocellular and canalicular cholestasis, giant cells, variable portal-periportal fibrosis, and absence of ductular proliferation [41]. In one study with 28 MVID children, 8 developed cholestatic liver disease—5 before and 3 after intestinal transplantation—the cholestasis improved

only after biliary diversion procedures or after removal of the intestinal graft. Increased absorption of circulating bile acids after intestinal transplant was the possible reason for aggravation of liver disease [10]. The link between MVID- and MYO5B-related cholestasis is complex and has been addressed in a recent review. Of the total 133 reported cases of MVID, cholestatic liver disease was present in 37%, and of MYO5B-related MVID, the prevalence was 54%. Contrarily, only 21% of patients with liver disease had diarrhea. The postulated reason was that MYO5B mutations in isolated liver disease may not cause sufficient loss of MYO5B function to result in intestinal failure. Thus, varied presentations are due to unequal effects of MYO5B mutations in the liver and intestine [16].

5.10 Hepatocellular Carcinoma in PFIC

Among the list of PFICs, children with BSEP deficiency are especially predisposed at a young age to develop HCC [33]. This happens due to persistent chronic inflammation leading to oncogenesis [44]. Studies from the USA and Europe showed that HCC occurs in 5–15% of children with BSEP deficiency at a young age (13–28 months) [6, 8, 31, 33]. Children with D482G mutations have less severe disease and portal hypertension, while HCC is common in those with non-D482G mutations [6]. From the cohort of 128 European children, single-strand conformation polymorphism analysis and sequencing of ABCB11 gene identified high risk of HCC (38% versus 10%) in children with the presence of 2 protein-truncating mutations [31]. From the recent NAPPED cohort with classification of BSEP into three categories, the prevalence of HCC in BSEP1, 2, and 3 were found to be 4%, 7%, and 34% [32]. Exome sequencing of the genomes of humans affected by BSEP and of *Mdr2* knock-out mice revealed that a very few somatic mutations accumulated over time in the cancer genes. This stands in contrast to adults with HCC as well as other malignancies where a number of mutations accumulate over a period of time. Further, in BSEP individuals and animals, there is massive gene amplification that affected components of signal transduction pathways, such as the ErbB, the PI3K/Akt, and the mitogen-activated protein kinase (MAPK) signaling pathways and, in particular, activators of c-Jun-N terminal kinases (JNK) [45]. Another study which provided further pathophysiologic insights into BSEP-mediated HCC showed that BSEP expression is severely diminished in HCC patients associated with alteration of farnesoid-X receptor (regulatory nuclear receptors) with increase in (FXR-α1/FXR-α2) ratio; the latter is induced by inflammation and may be reversible [46]. HCC has also been described in children with TJP2 deficiency again due to loss of hepatobiliary integrity and exposure of hepatocytes to detergent bile acids [40]. In MDR3 deficiency, HCC is rare but has been reported [47].

5.11 Diagnosis and Differentials

With the advancement of genetic testing, there is now a limited role of histology and electron microscopy. Immunostaining is still used to quantitate the severity of deficiency of BSEP and MDR3 proteins. With the development of genetic technology, most of these diagnoses are nowadays genetic based and have guided the clinicians for management and prognosis also. Next-generation sequencing technology makes it possible to sequence multiple genes, in multiple individuals, simultaneously. Its most comprehensive form is whole genome sequencing (WGS). Whole exome sequencing (WES) restricts sequencing to the exons of most genes, and is simpler than WGS. For cholestatic liver diseases, a targeted panel of genes can be sequenced which include all PFIC-related genes, genes causing Alagille's syndrome (JAGGED1 and NOTCH2), arthrogryposis, renal dysfunction and cholestasis syndrome, inborn errors bile acid synthesis, neonatal sclerosing cholangitis (Claudin-1 and DCDC2), and Niemann-Pick type C disease. WES with a targeted approach is essential before subjecting these children for LT [1].

5.11.1 Low GGT Versus High GGT Cholestasis

The mechanism for the low levels of GGT in serum of patients of most of the PFICs except PFIC3 is not very clear. The GGT enzyme is normally bound to the canalicular membrane by a glycosylphosphatidylinositol (GPI) anchor. In obstructive cholestasis as in biliary atresia, when excessive amounts of bile salts accumulate in the canalicular lumen under increased pressure, GGT is released from the membrane by detergent action and refluxes back into serum, possibly via leaky intercellular junctions. However, in all PFICs except MDR3 deficiency, alterations in lipid bilayer characteristics may lead to release of canalicular enzymes into bile. Immunohistochemical studies indicate that some canalicular proteins, including GGT and carcinoembryonic antigen, are poorly expressed at the canaliculus in PFIC1. On the other hand, in MDR3 there is cholangiocyte injury due to toxic bile acids leading to elevation of GGT [18]. Table 5.2 presents the differentials of low and high GGT cholestasis. In younger infants with low GGT, other differentials are bile acid synthetic defects, Aagenaes and arthrogryposis-renal dysfunction-cholestasis (ARC) syndromes, and metabolic enzyme defects. High GGT in very young infants requires biliary atresia to be excluded. Other causes of high GGT are Alagille's syndrome, sclerosing cholangitis (neonatal, primary, or secondary), congenital biliary stricture, inspissated bile duct syndrome, and autoimmune-overlap syndrome [2, 3]. The differentials should be looked up in proper context and background.

Table 5.2 Differential diagnosis of PFIC based on GGT and age of presentation

Low or normal GGT (FIC1/BSEP/TJP2/FXR/MYO5B)	High GGT (MDR3)
Bile acid synthetic defects (infant)	Biliary atresia (infant)
Aagenaes syndrome (infant or older child)[a]	Alagille's syndrome (infant or older child)[b]
ARC syndrome (infant)[c]	Inspissated bile duct syndrome (infant)
Metabolic disorders—Galactosemia, tyrosinemia, hereditary fructose intolerance (infant)[d]	Neonatal sclerosing cholangitis (infant)
	Congenital biliary stricture (infant)
	Secondary sclerosing cholangitis[e] (toddler)
	Cystic fibrosis (older child)
	Primary sclerosing cholangitis (older child)
	Overlap syndrome (older child/adolescent)

[a] Aagenaes syndrome, presents as lymphedema and cholestasis
[b] Alagille's syndrome: characteristic features are triangular facies, bulbous nose, murmur of peripheral pulmonary stenosis, butterfly vertebra, posterior embryotoxon, ductal paucity on liver histology
[c] ARC syndrome, arthrogryposis renal dysfunction and cholestasis syndrome, presents as cholestasis, diarrhea, renal tubular dysfunction, contractures
[d] Metabolic enzyme defects, usually infants are sick with coagulopathy, decompensation, diarrhea, and vomitings
[e] Secondary sclerosing cholangitis, usually develops in the setting of Langerhans cell histiocytosis, HIV, tuberculosis, or cystic fibrosis

5.12 Management

Management of all the forms of PFICs is focussed on control of pruritus, nutritional rehabilitation, and surveillance and management of decompensation, portal hypertension, and HCC (Fig. 5.3) [18].

5.12.1 Control of Pruritus

As discussed earlier that pruritus has multiple pathways, so numerous agents have been tried with a focus on promoting bile flow, decrease synthesis, binding, removal or replacement of toxic bile acids, altering metabolism of pruritogens, and modifying itch perception at the level of central or peripheral nervous system [22].

5.12.1.1 Role of UDCA

UDCA is normally present in only small quantities (<3%) in human bile and is formed by 7β-epimerization of the primary bile salt, chenodeoxycholic acid, through the action of colonic bacteria—b-position confers hydrophilic nature to UDCA. The compound has multiple beneficial effects when used in patients with cholestasis:

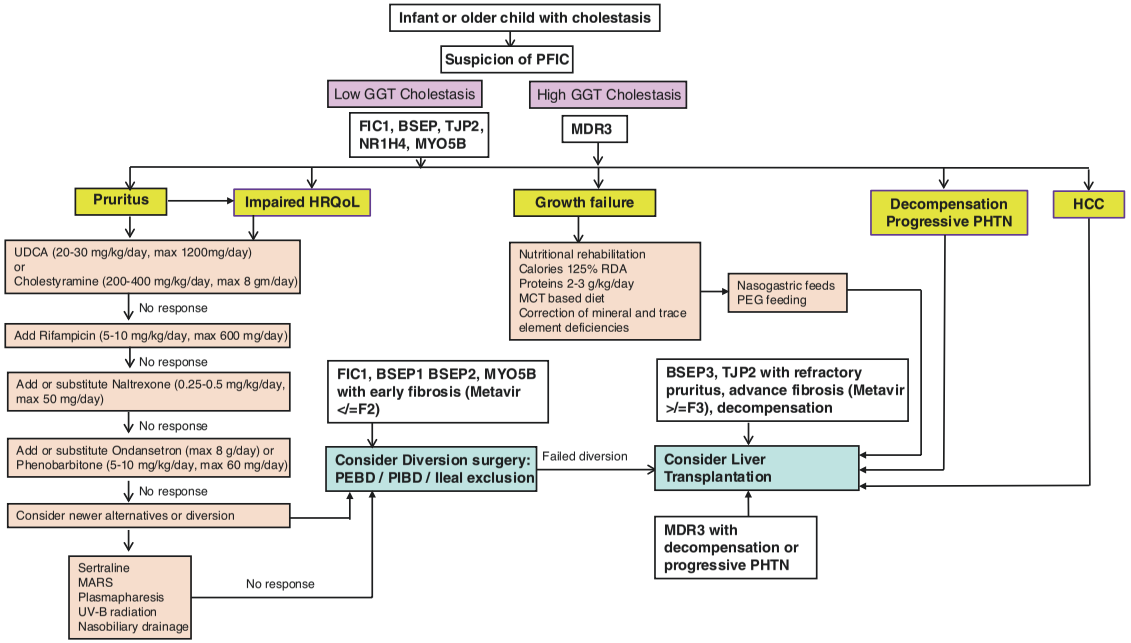


Fig. 5.3 Management algorithm for children with PFIC. Refractory pruritus not responding to medications should be considered for biliary diversion surgery. Indications for liver transplant are failed diversion, presence of decompensation, and progressive portal hypertension. Patients with BSEP3 (non-D482G, non-E297G), TJP2, and MDR3 and those with advanced fibrosis or HCC should be considered for transplantation [1–9, 11, 12, 14, 16, 32]. Abbreviations: *BSEP* bile salt export pump deficiency, *BSEP1* those with at least one copy of p.D482G or p.E297G (mildest phenotype with least severe disease), *BSEP2* those with at least one missense mutation (yet not p.D482G or p.E297G), *BSEP3* those with mutations causing completely nonfunctional protein or total absence of BSEP expression on immunostaining, *FIC1* familial intrahepatic cholestasis type 1 deficiency, *HCC* hepatocellular carcinoma, *HRQoL* health-related quality of life, *MARS* molecular adsorbent recirculating system, *MCT* medium-chain triglycerides, *MDR3* multidrug resistance protein-3, *MYO5B* myosin-5B protein mutations, *PEG* percutaneous endoscopic, *PHTN* portal hypertension, *RDA* recommended dietary allowance, *TJP2* tight junction protein 2 mutations, *UDCA* ursodeoxycholic acid, *UV-B* ultraviolet B

1. Replacement of toxic hydrophobic bile acids with hydrophilic UDCA.
2. Displacement of toxic bile acids from both the bile acid pool and hepatocellular membranes and thus direct stabilization of the hepatocyte membrane.
3. Direct hepatoprotective effect on hepatocytes.
4. Improvement of mitochondrial oxidative phosphorylation and prevention of mitochondrial membrane permeability transition.
5. Being poor at micelle formation and solubilization and poorly absorbed from the proximal intestine, a large amount of orally administered UDCA reaches the terminal ileum where it interferes with the absorption of endogenous, hydrophobic, and toxic bile acids—with oral administration UDCA concentration increases from 2 to 40%.
6. Direct hypercholeretic effect because of protonation of UDCA in the biliary ductule, and the protonated UDCA being lipophilic is rapidly absorbed by biliary epithelial cells prior to reaching the small intestine and is transported back to the liver (cholehepatic shunt).
7. UDCA also increases bile salt-independent flow through a direct effect on cholangiocyte calcium-activated chloride secretion, resulting in bicarbonate-rich choleresis.
8. Lastly, immunomodulatory role by reducing immunologic injury associated with some cholestatic liver diseases—reduced expression of abnormal HLA-1 class proteins on hepatocytes [18].

UDCA is therapeutic for early and milder forms of MDR3 disease (response in pruritus and improvement in liver biochemistry in up to 79%); however, the response rates are poor in most of the low-GGT cholestasis (<40–50%) [4].

5.12.1.2 Other Treatments

A stepwise management of pruritus is mentioned in Fig. 5.3 [18]. Phenobarbitone is also a choleretic which acts by increasing the bile acid-independent fraction of bile flow, enhancing bile acid synthesis, inducing hepatic microsomal enzymes, and increasing hepatic Na+-K+-ATPase activity. Bile acid-binding resins like cholestyramine or colestipol and colesevelam can be used to bind bile acids in the intestine, block enterohepatic circulation of bile acids, and thus decrease the pool. They also promote conversion of cholesterol into bile acids and thus stimulate choleresis. These drugs are given in juice or water either immediately before or after meals, when the bile secretion is maximal. However, the use is limited as other drugs should be avoided 2 h before or after resins, and the tendency to worsen fat-soluble vitamin deficiencies [18]. Rifampicin is a Pregnane-X receptor pathway and induces uridyl diphosphate glucoronosyl transferase 1A, CYP7A1, CYP3A4, MDR1, MRP2, and OSTβ, and thus helps in allaying pruritus in up to two-thirds of children with PFIC, although the response is partial in more than half of them [18, 20]. Various other agents act by modifying itch perception at the central level (opioid antagonists like naltrexone, nalmefene, and naltrexone) or at the peripheral level (sertraline and ondansetron) [18]. Despite medical management, 60–100% of patients with PFIC1 and 2 have persistent pruritus and require diversion surgery [4].

Table 5.3 Studies on diversion surgeries and their outcomes in PFIC

Author (year) [reference]	No. of patients	Type of diversion	Key findings
Whitington PF et al. (1994) [48]	33 PFIC	PEBD in 14 Partial ileal bypass in 2	PEBD: Relief of cholestasis completely (64%), partially (7%), secondary LT (29%)
Englert C et al. (2007) [49]	42 PFIC (26 type 2, 16 type 3)	17 PEBD	Successful PEBD in 29%, referred for LT (76%)
Yang H et al. (2009) [50]	11 PFIC 3 Alagille's	PEBD	Pruritus relieved completely in 50%, partially in 25%, bile salts and growth improved in most patients, bile salts reduced in those with early fibrosis but not with advanced fibrosis
Erginel et al. (2018) [51]	6 PFIC	PIBD	Decrease in serum bile acids, bilirubin, and transaminases, improvement in pruritus 5 (83%) symptom-free at 6-year follow-up, 1 had refractory pruritus, died after LT
Bull LN et al. (2018) [12]	102 PFIC (60 FIC1, 42 BSEP)	57 PEBD 6 ileal exclusion 57 LT	Sustained improvement in pruritus: No difference between FIC1 or BSEP, BSEP common D482G or E297G mutations showed 76% response & BSEP other mutations 33% (OR for sustained response = 8.1) Median time from PEBD to LT: BSEP common D482G or E297G mutations > FIC1 > BSEP other mutations Progression to cirrhosis: BSEP other mutations (33%) > BSEP common D482G or E297G (9.5%) mutations > FIC1 (0%) Need for LT: BSEP other mutations (70%) > FIC1 (27%) > BSEP common D482G or E297G (16%)
Van der Woerd WL et al. (2015) [52]	4 PFIC 1 Alagille's	TBD	PFIC: Marked improvement clinically and biochemically Alagille's: Pruritus improved but cholestasis persisted

Abbreviations: *BSEP* bile salt export pump deficiency (PFIC2), *FIC1* familial intrahepatic cholestasis type 1 (PFIC1), *LT* liver transplantation, *PEBD* Partial external biliary diversion, *PIBD* partial internal biliary diversion, *PFIC* progressive familial intrahepatic cholestasis

5.12.1.3 Surgical Diversion

Refractory pruritus not responding to medical management often requires surgery in the form of biliary diversion. Table 5.3 presents the outcomes of diversion surgeries in children with PFIC1 and 2. Diversion surgeries are indicated for low-GGT cholestasis and Alagille's syndrome and not for MDR3 deficiency [48–51]. Patients should be considered for diversion only in the absence of advanced fibrosis (Metavir <F3, Ishak <F4) [50]. The basis for all these procedures is to interrupt enterohepatic circulation of bile salts, and thus allay pruritus and improve liver biochemistry. Various surgical procedures used are mentioned below:

1. Partial external biliary diversion (PEBD): This is the most often used diversion procedure. In this procedure, the bile is diverted from the gallbladder to the jejunal conduit (10–15 cm in length) connecting the gallbladder to the abdominal wall via a permanent cutaneous stoma, thus interrupting the enterohepatic circu-

lation of bile acids. Bile collected in the stoma bag (120–200 mL/day) is discarded [18]. There are reports of creation of PEBD laparoscopically [53]. PEBD has been shown to improve growth and liver biochemistry, reverse and prevent progression of fibrosis, and thus reduce disease progression in up to 80% of children with PFIC1 and 2 [48–50]. However, the procedure may fail in 25–71% [4]. From the largest multicentric cohort of children, median ages at PEBD for FIC1 and BSEP were 1.6 and 2.3 years with sustained improvement in pruritus in 57% and 44%. In the BSEP group, the response was better in those with D482G and E297G mutations [12]. Specifically, in the BSEP cohort of patients, surgical diversion is associated with increased survival in those with BSEP1 or 2 (hazard ratio 0.50) than in those with BSEP3. Further, a low serum bile acid concentration <102 μmol/L or decrease of at least 75% shortly after diversion surgery predicted survival with native liver ≥15 years post-diversion [32].

2. Partial internal biliary diversion (PIBD): As PEBD causes persistent biliary fistula and is cosmetically not a good surgery, various types of internal biliary diversion surgeries have been devised which are more acceptable to the patients and their families. Some of these procedures are cholecystojejunocolonic, cholecystoileocolonic, or cholecystoappendicocolonic anastomosis or cholecystocolostomy. In the cholecystojejunocolonic anastomosis, 15–20 cm jejunal conduit is anastomosed proximally in a terminolateral fashion to the gallbladder and distally to the colon. PIBD can also be performed laparoscopically. Although cosmetically favorable, PIBD carries risk of complications like intestinal obstruction, ascending cholangitis, and osmotic diarrhea due to increased bile acid load to the colon [18, 51].
3. Ileal bypass or exclusion: In this procedure, there is construction of side-to-side ileocolic anastomosis leading to diversion of bile acids directly into the colon. This is an alternative rescue option to PEBD and should be offered cautiously, only to patients who cannot benefit from PEBD [12, 18].
4. Total biliary diversion (TBD): In PEBD, the common bile duct remains intact, so a small fraction of the bile is still excreted into the duodenum, which is reabsorbed in the terminal ileum, contributing to persisting cholestasis and pruritus. TBD has been done in children with refractory pruritus and has been shown to completely abolish or significantly reduce pruritus. The study proposed TBD as a surgical technique for non-cirrhotic patients with low-GGT cholestasis with failed PEBD or PIBD [52]. Moreover, TBD has been advocated for children with FIC1 disease who develop intestinal symptoms after LT and is sometimes done at the time of LT [54].

5.12.2 Nutritional Rehabilitation

Most of these children have poor growth due to persistent cholestasis, increased catabolic state, anorexia, splenomegaly due to portal hypertension, and presence of ascites. These children need supplementation with fat-soluble vitamins 3–5 times of recommended dietary allowance (RDA), water-soluble vitamins 2–3 times of RDA,

calories 125% of RDA based on weight for height at 50th centile, and proteins 2–3 g/kg/day. Medium-chain triglycerides should comprise 60–70% of the calories provided by fats in the diet—these are better absorbed in children with cholestasis, reduce steatorrhea, improve energy balance, and promote growth. Essential major and trace elements are needed in children with suspected deficiencies: calcium (25–10 mg/kg/day up to 800–1200 mg/day), phosphorus (25–50 mg/kg/day up to 500 mg/day), magnesium (1–2 meq/kg/day), zinc (1 mg/kg/day), selenium (1–2 μg/kg/day), and iron (5–6 mg/kg/day). Night-time drip feeds as nasogastric feeds are required in children with poor weight gain. Some patients may need an insertion of percutaneous endoscopic gastrostomy tube [18]. These children need careful surveillance every 2 weeks for growth to decide the need for nutritional intervention.

5.12.3 Liver Transplantation

Various indications for LT in PFIC are decompensated end-stage liver disease, refractory pruritus, unsuccessful biliary diversion, and severe growth failure [4, 6, 8, 12]. From the multicentric European and American cohort of patients with PFIC1 and 2 with 102 children (60 FIC1 and 42 BSEP deficiencies), 57 children required LT. It was shown that there was longer survival with native liver without developing cirrhosis in children with FIC1 deficiency and those with BSEP D482G or E297G mutations in comparison with those with other BSEP mutations. Transplantation improves cholestasis in all group of patients. Overall outcomes were good with 5% mortality and 9% retransplantation. Five BSEP and four FIC1 patients received living-donor LT—seven from obligate heterozygous parents—however the outcome was not different. Graft steatosis and diarrhea were more common in FIC1 than BSEP patients (90.5% and 81% versus 6.4% and 7%). Also, there was mild elevation of transaminases and platelets in FIC1 patients after LT. FIC1 patients remained at lower end of their growth centiles 1 year post-LT (35% and 31% above third centile for weight and height) in contrast to BSEP patients (88% and 90% above third centile for weight and height), and had a trend toward delayed puberty [12].

5.12.3.1 Post-Transplant Diarrhea and Graft Steatosis in FIC1 Disease

There is high prevalence of diarrhea and graft steatosis (73%) progressing to steatohepatitis (64%) within a year of transplantation in FIC1 patients. The possible explanation for exacerbation of diarrhea post-LT is because ATP8B1 gene product dysfunction is decompensated on the intestinal side after continuous restoration of bile flow and bile acid secretion leading to high bile acid load in the intestine causing refractory diarrhea and subsequently graft steatosis. This is also explainable by the fact that the diarrhea and steatosis improve with usage of bile acid absorptive resin. Another explanation for diarrhea is exocrine pancreatitis insufficiency [55]. Total biliary diversion surgery after or at the time of LT helps in alleviating diarrhea in these children and is used by some centers [54].

5.12.3.2 Post-Transplant Recurrence of Disease in BSEP Deficiency

Some children develop recurrence of BSEP disease after LT. This happens more often in children with splice-site and premature stop codon mutations with complete absence of BSEP before LT leading to insufficient auto-tolerance against BSEP after LT. These allo-reactive antibodies are directed specifically against one extracellular loop of the BSEP protein, and which block the function of the normal protein in the transplanted liver. Due to humoral nature of this phenomenon, the derangements in liver functions in these children are sometimes refractoriness to changes in immunosuppressive medications [56, 57]. There are reports on successful usage of B-cell depletion therapies, i.e., combination of rituximab (monoclonal anti-CD20 antibody), intravenous immunoglobulin, and plasmapheresis, followed by resolution of recurrence [58].

5.13 Surveillance

Surveillance for decompensation and portal hypertension: Children with BSEP and TJP2 mutations need close monitoring for presence of decompensation. Regular outpatient visits every 4–6 weeks are required for early detection of decompensation [6, 8, 9]. FIC1 and MYO5B children may need less frequent monitoring [6, 8, 16]. Screening for varices should be performed in all children with persistent splenomegaly and/or platelet counts <100,000/mm^3. MDR3 children, who usually present late, need careful follow-up for decompensation as well as portal hypertension. Repeat endoscopy with absent, small, or large varices should be performed at 6-, 6-, and 3-monthly intervals.

Surveillance for HCC: BSEP deficiency children, especially with BSEP3 (completely nonfunctional protein or total absence of BSEP on immunostaining) and those with TJP2 mutations require 3-monthly surveillance for HCC with ultrasound and serum alfa-fetoprotein levels. Children with cirrhosis with other types of PFIC need 6-monthly surveillance for HCC [44].

5.14 New Treatment Targets

Table 5.4 shows various newer treatment approaches for children with PFIC based on modulating action of bile acids (PPAR-α, TGR5 agonists), reducing intestinal uptake of bile acids (ASBT inhibitors), removal of pruritogens (ultraviolet B, plasmapheresis, Molecular adsorbent recirculating system, MARS), reducing synthesis of bile acids (FXR agonists), or altering metabolism of pruritogens (PXR agonists, Ultraviolet-B) [18, 20, 59–64].

Table 5.4 Newer potential treatment targets for children with cholestatic liver diseases including PFICs [20]

Therapeutic agents	Target	Action	Remarks
Obeticholic acid [59]	FXR	Agonist	Used in adult patients with PBC, increased pruritus (POISE trial), improved inflammatory markers, ALP and bilirubin, decreased C4 bile acids
All-trans retinoic acid	RXR	Agonist	Therapeutic benefits not yet proven
Bezafibrate [60] Fenofibrate Ciprofibrate	PPARα	Agonist	Used in adult patients with PBC (BEZURSO trial), improved liver biochemistry, fatigue, pruritus, and fibrosis; insertion of MDR3 into canalicular membrane, anti-inflammatory effects
Rifampicin Statins Corticosteroids	PXR	Agonist	Induction of CYP7A1, UGT1A1, MDR1, MRP2, MRP3, OSTβ, rifampicin improves itching
NGM282 (FGF19 analogue) [61]	FGFR4	Activator	Multiple roles in bile acid, carbohydrate, and lipid metabolism, used in NASH patients with improvement in liver fibrosis
Int777	TGR5	Agonist	Inhibits proinflammatory cytokine production, migration and phagocytic activity of macrophages and Kupffer cells, improves intestinal barrier function
Maralixibat [62]	ASBT	Inhibitor	Inhibits bile acid absorption, one-point reduction in pruritus when used in Alagille's syndrome
Vitamin D	VDR	Agonist	Stimulation of bile acid detoxification enzymes (CYP3A4 and SULT2A1)
norUDCA	–	Choleretic	Cholehepatic shunting allows targeted anti-inflammatory, anti-fibrotic, and antiproliferative effects to injured ducts
MARS [63]	–	Removes pruritogens	Used in adults with median two sessions (1–5), reduces pruritus and bile acids
Ultraviolet-B light phototherapy [64]	–	Chemically modify pruritogens	Works at a wavelength of 290–320 nm, Used in adults, 60% reduction in pruritus, Risk of skin cancer, keratitis, cataract, infertility

Abbreviations: *ALP* Alkaline phosphatase, *ASBT* Apical sodium bile acid transporter, *CYP* Cytochrome P enzyme, *FXR* Farnesoid X receptor, *FGF19* Fibroblast growth factor 19, *FGFR4* Fibroblast growth factor receptor 4, *MARS* Molecular adsorbent recirculating system, *MDR* multidrug resistance protein, *MRP* multidrug resistance-associated protein, *NASH* non-alcoholic fatty liver disease, *OST* organic solute transporters, *PPAR-α* peroxisome proliferator-activated receptor alpha, *PXR* pregnane X receptor, *RXR* retinoid X receptor, *SULT2A1* sulfotransferase family 2A member 1, *TGFR5* transforming growth factor receptor 5, *UDCA* ursodeoxycholic acid, *UGT* uridylylglucoronosyl transferase, *VDR* vitamin D receptor

5.15 Conclusion

PFICs are autosomal recessive heterogenous group of cholestatic disorders characterized by pruritus, growth failure, hepatosplenomegaly, and poor quality of life. With advancement in genetics and basic science research, these disorders are now

well identified and characterized. Genetic-based classification helps in guiding management and prognosis of these children. Surgical diversion techniques serve as a definite or bridging treatment for these children. Liver transplantation offers complete cure for these entities but with risk of diarrhea in FIC1 and recurrence of disease in BSEP. Future research in this field is ongoing to identify newer genetic entities causing cholestasis and therapeutic agents directed against the hepatotoxic effects of bile acids.

Editorial Comments

Progressive familial intrahepatic cholestasis (PFIC) is one of the causes of neonatal cholestasis. Unfortunately, the condition often does not get due attention for a quick diagnosis and timely referral to an appropriate center. Not infrequently the child with suspected PFIC has developed cirrhosis of the liver by the time the child reaches a specialist. If the outcomes are to improve, this will need to change.

These children present with features of neonatal cholestasis, which has many physiological and pathological causes such as infection, biliary obstruction, genetic and metabolic diseases, endocrinopathies, drugs, neonatal hepatitis, etc. The common conditions are biliary atresia (25%–55%) and Alagille syndrome (2%–14%).[1] Children born prematurely have a higher incidence due to various causes. Therefore, all these causes need to be excluded before entertaining a diagnosis of PFIC.

The practical approach while approaching an infant presenting with neonatal cholestasis is to ascertain the type of jaundice, direct or indirect. Direct or conjugated hyperbilirubinemia indicates biliary-hepatic problems like biliary atresia (the commonest cause) or bile transport disorders like PFIC. The liver enzyme levels, ALT, AST, and alkaline phosphatase, are raised in almost all patients. Serum gamma-glutamyl transpeptidase (GGT) levels are helpful in such cases; while GGT is elevated in biliary obstruction, it is low or normal in all variants of PFIC (1, 2, 4, and 6) except PFIC-3 in which it is elevated.[2]

The further investigations done to clinch the diagnosis are ultrasonography, liver elastography, nuclear scan, cholangiography (usually preoperative), and liver biopsy.[2] However, there is a paradigm shift in the approach with the availability of genetic studies.[2]

Once a diagnosis is made, these children should be managed with pharmacotherapy and adequate nutrition. Those who respond should continue with it, but those who do not should be further evaluated and considered for surgical alternatives discussed in the article. Those unfortunate children who do not respond and develop hepatic decompensation or hepatocellular carcinoma should be considered for liver transplantation.[3]

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Chapter 6
Training and Credentialing in Multi-Organ Retrieval: Indian Perspective

Karthik Raichurkar and Sonal Asthana

6.1 Introduction

There is a huge gap in the need and supply of organs for donation in India. It is estimated that about 20,000 people need a liver transplant each year because of end-stage liver disease [1], but about 2000 transplants are done each year, which is only 10% of the actual need [1]. The incidence of end-stage chronic kidney disease (CKD-5) in India is estimated to be around 180/million population [2] and about 20% of these cases receive a renal transplant [3]. Annual requirements for heart–lung transplants are estimated to be between 5000 and 10,000 with fewer than 10% of patients being fortunate enough to receive one [4]. These numbers are conservative; the actual numbers are likely to be much higher.

Deceased organ donations have the capability to cover the needs and fill the gap of demand and supply chain for organ transplant [5]. In the early era of transplantation, the lack of deceased organs led to most programs developing and becoming proficient in living-donor transplantation. India continues to have some of the largest volumes among living-donor programs in the world with skilled surgeons and excellent technical results. However, this scenario started changing toward the end of the first decade in the twenty-first century. With increase in donations after brain death (DBD), particularly in the southern states led by Tamil Nadu, there has been a newfound emphasis on organ transplants from deceased donors. The national organ donation rates currently are around 0.8/million population, which is a tenfold improvement in a decade. Furthermore, an increasing number of donations are occurring in smaller cities [5], which brings in logistical challenges of safe retrieval and transport. This number and these decentralized trends are likely to increase in the coming years.

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Organ retrieval forms an important part of any transplant. Traditionally, transplant surgeons in India have trained in organ recovery from the western countries (USA/UK), where deceased donor transplant programs started much earlier. Training in transplant surgery and multi-organ retrieval has been fostered by the institution of surgical fellowships all across the world. The structuring and the curriculum of such training programs has been continuously evolving [6, 7]. In India, though such fellowships have existed since a decade, there is no clear consensus on what curriculum and training protocols are to be followed and who qualify for undergoing such training in the field of organ retrieval and transplant. This process of training and credentialing of multi-organ retrieval in India has started evolving, and we aim to give a clearer picture on the needs and the way forward in such a process.

6.2 Who Should Be Trained for Multi-Organ Retrieval?

In the western scenario, fellowship programs started in early 1990s, and systematic training offered in these programs led to the availability of surgeons who could perform multi-organ retrieval. The fellowships are offered to residents who have completed their general surgery rotation. The residents either choose abdominal organ transplant or a thoracic organ transplant training according to their preference. The abdominal transplant fellowships train surgeons in retrieval of the kidney, liver, pancreas, and small bowel, while the thoracic fellowships train surgeons in retrieval of the heart and lungs. Transplant is chosen as a separate sub-speciality after general surgical training. However, in India, there are organ-specific sub-speciality branchings after general surgery training. Transplantation as a separate sub-speciality has not yet been recognized as per the National Medical Commission (NMC) norms. Most fellowship programs offer training to surgeons who have completed their sub-specialty training for further refinement in the transplant of the organ related to the respective sub-specialty. For example, heart transplant fellowships are offered to surgeons who have completed their MCh in cardiothoracic surgery, and liver transplant fellowships are offered to surgeons who have completed their MCh in surgical gastroenterology. The NMC specifies the minimum qualification required to get into training for such fellowships to be MS Gen surgery followed by 3 years' experience in postgraduate teaching as a senior resident or MCh is their respective fields [8]. The same was specified by the Liver Transplant Society of India (LTSI) for qualifying for a fellowship in liver transplant [9].

In India the geographical unequal distribution of available brain-dead cadavers and trained personnel for retrieval poses a unique problem in training only fellows for retrieval. The additional training of surgeons in the periphery to retrieve organs can save valuable time and improve the donor pool. The declining of transplant teams to retrieve an organ in the periphery for logistic reasons can be overcome if someone in the area can be trained for the purpose. There is evidence to suggest that when such organs retrieved by community surgeons are transplanted, the long-term

functions are not significantly different [10]. Similar findings were present in a study done in 1980, where 82 community hospital cadaver kidney retrieval teams were trained during a 10-year period. In the last 5 years, these surgeons were involved in retrieval of multiple organs. They compared the functioning of grafts retrieved by community surgeons versus functioning of grafts retrieved by the in-house transplant surgeons. The comparison did not show any significant difference in functioning grafts. Based on this observation they concluded that with continuing education and quality control, community hospital retrieval teams can provide kidneys satisfactory for transplantation, even when working with multi-organ retrieval teams.

Such training of surgeons in the periphery can also help in decreasing the manpower required at specialized transplant centers easing them of the financial expenses and decreasing the cost of running a transplant program. A Bulgarian study looked into this aspect in 1996 [11]. Their model of regionalization of organ procurement proved to be effective in achieving a high quality of organ retrieval and a reduction in personnel requirements for the transplant centers. In addition to this, the team was able to reinforce positive response from the donor hospitals leading to increase in the number of cadaveric donations in the region. Hence, training of peripheral surgeons in multi-organ retrieval has several advantages. It can overcome the logistic difficulty of a team's inability to reach in time for a multi-organ retrieval. It can ease the financial burden on transplant teams and at the same time reinforce increase in cadaveric donations in peripheral regions under the guidance of these trained surgeons. Relevant financial savings can result from reduced on-call duties and minimized traveling costs.

Not only does this help in increasing the donor pool, it also helps in fostering an increase in the overall number of transplants happening all across the country. The future training programs should take into consideration these issues and offer training of surgeons in multi-organ retrieval, to not only surgeons interested in pursuing transplant as their specialty but to surgeons practicing in the periphery as well, to aid the growth of transplant-related activity.

There might be concerns about the safety of the retrieved organs when a regional surgeon retrieves an organ. However, enough data is available to suggest that such a process is safe, and no important injuries occur to the organs during retrieval by trained regional surgeons [10, 12].

6.3 Training Methodology: How to Train?

6.3.1 Fellowship Programs

Most western centers have a graded method to assess training in the fellowship programs. They have a set number of retrievals to be carried out under supervision with expert assistance before being allowed to do operations independently. The

surgeons undertaking retrieval should have complete knowledge of the anatomy, technique of in situ cold perfusion, and safe cold dissection techniques to avoid injury to the vascular structures/organs. Among the common causes for bad outcomes following transplantation are injuries that happen to the organs during retrieval due to inexperience of the retrieval surgeon. Most European programs specify the following minimum numbers for credentialing in multi-organ retrieval [13].

Organ to be retrieved	As assistant surgeon	As main surgeon under supervision
Kidney	20	20
Pancreas	10	02
Liver	10	10

The fellowship programs in India, as of now, do not have such defined training modules in place as in the western world. The LTSI formed in 2017 does aim to provide a basic structure to the recommended training protocols to be put in place. A consensus conference held at AIIMS in September 2015 (training in liver transplant) [14] specified the following requirements for credentialing as a liver transplant surgeon:

1. Junior consultant
   (a) Multi-organ retrieval: see 10 and assist 10.
   (b) At least 3 years' training in hepatobiliary surgery.
   (c) Training in vascular surgery.
   (d) Duration of fellowship: 1 year for DDLT and 2 years for LDLT.
2. Senior consultant
   (a) At least 5 years' training in hepatobiliary surgery.
   (b) 2-year junior consultant position in a transplant center.

There is a need to standardize training protocols all across the nation, to make training in multi-organ retrieval more effective. This will lead to further increase of transplant activity all across the nation.

6.3.2 Didactic Lectures/E-Learning and Cadaveric Workshops

Surgeons can be taught the steps of organ retrieval using videos and didactic lectures on the steps involved. There is evidence on the effectiveness of such learning if it is further backed up by practical sessions from the European Union where the method was used to transfer expertise to the nations which lacked exposure to organ retrieval [13]. The methodology is certified by the European Society of Organ Transplant (ESOT). It is open to candidates from all over the world, organized in the form of a 2-day workshop. The curriculum includes an E-learning tool developed by

the Leiden University Medical Center, the University Medical Center Groningen, and the Dutch Transplant Foundation [15], and a competence assessment form signed by the tutor evaluating the technical skills of the trainee. In addition a master class on retrieval surgery (with hands-on sessions and procedures of organ recovery on preserved human bodies) is carried out. The experience showed the great potential for sharing best practices and for direct transfer of expertise to surgeons not exposed to the process of organ retrieval. The final goal is to not only provide a national training to all interested surgeons but also to improve the quality and safety criteria of organs to be transplanted. The process can sharpen the understanding of anatomy and the steps involved in multi-organ retrieval to those surgeons lacking in understanding of the whole process.

We have a similar experience of organizing cadaveric workshops across the country and involving surgeons with didactic lectures followed by training in organ harvesting in preserved human cadavers with good results [13, 15, 16].

E-learning and simulations on pigs have been used in Japan to train surgeons in multi-organ retrieval in view of less availability of deceased donors [17]. The method has been shown to be successful in helping surgeons in the real-life scenario of organ procurement. Similar programs have been developed in India, but their impact is yet to be studied.

6.3.3 Our Experience

A structured training workshop on organ retrievals from deceased donors was developed along with surgeons from Oxford University and MOHAN Foundation. This course was modeled on the National Organ Retrieval workshop conducted by Oxford University for the UK National Health Service Blood and Transplant (NHSBT), which is a required training for any surgeon before becoming part of the National Organ Retrieval Service (NORS) teams, which are mandated to carry out organ recoveries in designated regions in the UK. The course was modified for Indian relevance by inputs from the National Organ and Tissue Transplant Organization (NOTTO) and the MOHAN Foundation, to include a primer on Indian law and the process as developed by different states in India. This 2-day workshop included a day of didactic training, followed by a hands-on structured retrieval training process supervised by instructors. There was an organ recovery demonstration by senior teaching faculty, which was live cast on social media as a means of dissemination of organ retrieval procedure.

This course has been conducted on an annual basis for the past 5 years and has trained more than 150 surgeons in the process of organ recovery. The liver webcast has been viewed in 37 medical colleges. Variations of this course have been incorporated into surgical conference workshops conducted by national professional bodies. We have documented an increased interest in web viewership over time (Fig. 6.1). A follow-up study of course participants revealed that workshop attendees had been responsible for 250 additional organ recoveries after training (Fig. 6.2).

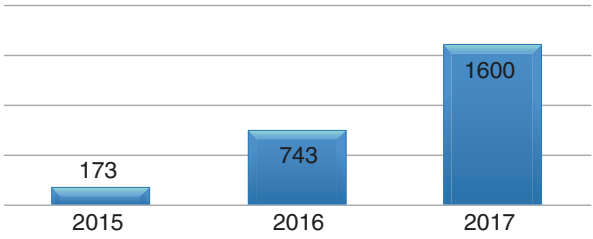

Fig. 6.1 Number of web views of the program

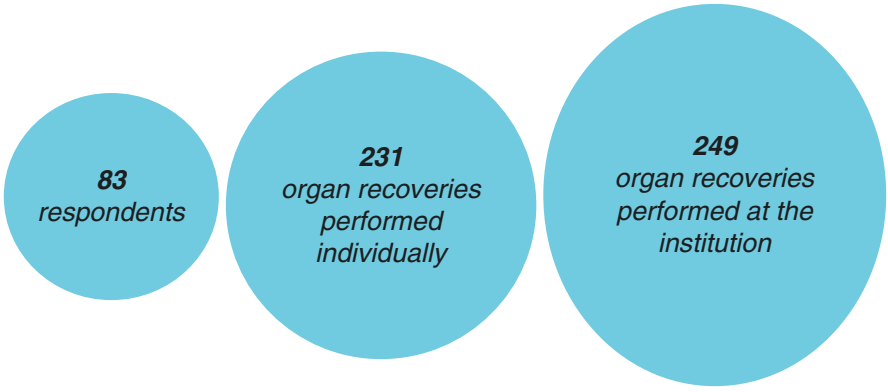

Fig. 6.2 Impact of national organ retrieval workshop (2015–2017)

Two cardiac surgeons had gone on to establish independent cardiac transplant programs in the public sector [18].

Not all surgeons (particularly those practicing in the periphery) would have the time and inclination to get trained through a fellowship program. This form of training for a multi-organ retrieval accounts for short-term training for such surgeons. It can add value to the transplant programs as already discussed above. However, it has to be kept in mind that the quality of teaching should be given paramount importance. We have been able to show from our data that surgeons can be trained in such a methodology without compromise on the quality of retrievals being performed. The LTSI aims to further refine the techniques involved in the teaching modality [9].

There is enough data to suggest that such methods of training on cadaveric modules are effective in imparting training in multi-organ retrieval [13, 15, 16].

6.3.4 Collaboration Between Centers

There is difference in volumes across different centers in India, with major differences in the public and private sectors. A majority of transplant activity in India happens in private sector hospitals, which are out of reach for most India patients. Though renal transplants are happening regularly in a few government hospitals,

liver, heart, and lung transplants are more commonly being done in private hospitals. Very few government hospitals have the infrastructure and manpower to run a full-fledged transplant program, given the large competing burdens on time and resources. With improvement in knowledge, attitude, practices, and help of nongovernmental organizations, the government hospitals particularly in southern states have emerged as centers for generation of deceased donors and contribute to the state pool of donors [5]. Mentorship of public hospital teams by established private hospitals in training the doctors involved in multi-organ retrievals/transplant surgery is desirable as it can facilitate the development and training of transplant programs in teaching hospitals. This will go a long way in improving access to transplant, and shared ownership, which is so critical to developing a positive outlook to organ donation among the general public.

Centers specializing in DDLT particularly in the south can collaborate with the hospitals doing predominantly LDLT. Both will be benefitted by the exchange of knowledge. The consensus meeting on training in liver transplant stressed the need for such collaboration between different centers [14].

6.3.5 Training in Vascular Surgery

Training in vascular surgery has beneficial effects for transplant fellows [7]. Higher confidence in handling aortic cannulation and bleeding control practices can have positive influence in handling a multi-organ retrieval better. A short-term training/rotation in a high-volume vascular surgery unit is recommended for retrieval surgeons. Traditionally, transplant fellows have been trained in vascular access procedures such as an arteriovenous (AV) fistula for dialysis [19]. Exposure to such procedures not only improves confidence in handling bigger vessels without fear but also improves skills of vascular anastomosis.

6.3.6 Other Aspects to the Trainee

A trainee undergoing a multi-organ retrieval needs to be motivated in many other aspects. Most retrievals happen at night and on weekends/holidays. No other field encompasses the principles of knowledge, ethics, compassion, and technical skills than the field of transplant surgery. The surgeon should have a sort of "vocation" for the field [20]. Organ harvesting setting is a good proof of adaptability, mostly during night time, often in small hospitals with operating room nurses unfamiliar with the procedure, sometimes waiting for some colleagues or delaying the surgery. The surgeons need to be mentally adaptable to these situations. At the same time, they need to be given proper incentives both professional and financial. The future training programs should incorporate all these aspects in training and credentialing of such surgeons.

6.4 Who Should Credential Multi-Organ Retrieval?

Fellowships in the USA are credentialed by the American Society of Transplant Surgery (ASTS) and in the UK by the NHS. In India the formal training degrees are recognized by the NMC. As of now, there are no NMC-recognized formal training courses in the field of transplant surgery/multi-organ retrieval. Though a few fellowships are credentialed by the National Board of Examinations (NBE-FNB in transplant) and a few state universities (MGR University in Tamil Nadu for liver/renal transplant fellowships), much of the credentialing is happening at the level of hospitals and individual surgeon-based experience certificates. The LTSI has taken up the responsibility of starting fellowship programs and standardizing training which is yet to take shape [9]. It is a need of the hour to have a common curriculum and standardize training across the entire nation and start programs credentialed by the NMC, if we are to attract more surgeons for formal training. Such steps can go a long way in bridging the gap in the need and supply chain of trained personnel for multi-organ retrieval.

6.5 Conclusion

In conclusion the process for training and credentialing multi-organ retrieval surgeons in India needs to be standardized. We have come a long way in the establishment of transplant programs. Further refinements in training modules to the target surgeons will help in widening the reach of transplant programs all over India. A wider spread of organ recovery centers will require the need to create and train a "retrieval surgeon," to be fully able to utilize the potential of India's increasing organ donation rates.

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- Dr. Harsha Jauhari, Advisor, NOTTO
- Dr. Vasanthi Ramesh, Director, NOTTO

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Chapter 7
Robotic Surgery in Living Donor Liver Transplantation

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7.1 Introduction

Minimally invasive surgery (MIS) carries with it the allure of smaller incisions and faster postoperative recovery and has permeated almost all surgical specialties. Nevertheless, MIS has remained unpopular among hepatic surgeons, who perform only a minority of hepatic resections by MIS. The difficulty of access for fine dissection in deep anatomical locations, concerns about limited maneuverability, risk of major bleeding during transection and non-availability of appropriate instruments specific to hepatobiliary surgery have perhaps led to the cautious adoption of MIS in hepatectomies. Live donor hepatectomy has been regarded as one of the most demanding and challenging pinnacle of hepatobiliary surgery, and adoption of minimally invasive techniques in this area has been particularly slow. A donor in living donor liver transplantation is a healthy individual, and surgeons have understandably and rightly been cautious in using laparoscopy or robotics for donor hepatectomy. Recent studies in few high-volume centers have shown that minimally invasive surgery is comparable to open hepatectomies, albeit with a longer learning curve.

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7.2 Evolution of MIS and Robotic Surgery in Liver Transplantation

Starting with the first laparoscopic cholecystectomy performed in 1987 [1], adaptation of laparoscopy has leaped forward at dizzying speed, despite being limited by rigid instruments with fulcrum effect, 2D vision, poor ergonomics and heavy dependence on the assistant for camera vision. Laparoscopic hepatectomy for liver tumors was reported as early as 1990. In minor liver resections, laparoscopy was associated with lower postoperative morbidity (transfusions, pulmonary embolism, and wound infection), shorter hospital stay, and decreased blood loss with comparable oncological outcomes and survival as its open counterpart [2, 3]. The Louisville Statement (consensus conference organised in Louisville, Kentucky, USA, in 2008) draws the indication of minimally invasive liver resection for solitary lesions 5 cm or less, in segments 2, 3, 4, 5 and 6, minor segmentectomies and left lateral sectionectomy. It suggested that minimally invasive major hepatectomies should be attempted only in specialised centers with experienced surgeons [4].

The introduction of the Da Vinci surgical system has definite technical advantage over laparoscopy with articulated endowristed instruments (7 ranges of motion versus 4 degrees in laparoscopy), removal of fulcrum effect, image stabilisation, built-in ultrasonography, indocyanine green cholangiography, tremor filtration, three arms as well as camera under the surgeons' control and superior 3D vision. Robotic console thus offers better precision and dexterity especially for complex suturing [5]. The major advantages of the robotic system are during hilar dissection, hepatocaval dissection and parenchymal transection in right hepatectomies [5]. Precise intracorporeal suturing has facilitated complex biliary reconstruction and managing difficult bleeding deep inside hepatic parenchyma [6]. Robotic surgical system has enabled minimally invasive posterior-superior segmental and caudate resections in difficult-to-reach positions. Choi et al. demonstrated that complex liver resections can be safely performed using robotic surgical system, concluding however that large multicenter studies are needed to define the safety and feasibility of this approach. Comparative studies have shown similar blood loss, morbidity, mortality and hospital stay but prolonged operative times and increased costs in robotic hepatectomies [6–10].

Donor hepatectomies are unique in the prospect that the safety of the volunteering healthy individuals is paramount along with the need to minimise ischemic time and surgical trauma to the liver on both sides of the transection. In India, deceased organ donation rates are abysmal compared to other countries in the world, and living donors form the mainstay of most transplantation units. Concerns about the safety of healthy volunteers have understandably prevented widespread adoption of newer minimal invasive procedures. At the same time, 30%–50% of donor morbidity is associated with abdominal wall trauma, hernia, bowel obstruction and abdominal discomfort [11]. Efforts to reduce the postoperative morbidity have led to the adoption of MIS in donor hepatectomies. Laparoscopic left donor hepatectomy has the potential to become a future standard, but right donor hepatectomy remains a

challenge [12, 13]. After the first reported laparoscopy-assisted donor right hepatectomy in 2006 [14], most studies have reported high conversion and complication rates [15] or have included hand-assisted procedures. Three international consensus meetings have been held in Louisville, Morioka and Seoul. Consensus guidelines proposed at meeting held in Southampton have stated that laparoscopic left lateral segmentectomy for living donor liver transplantation is the gold standard and provides more favorable conditions compared to the right hepatectomy [16]. Laparoscopic right donor hepatectomy has been proven as safe but only in a few expert centers, and the benefits are not only cosmetic (Fig. 7.1) and an earlier return to work but may additionally increase the number of potential donors [17]. The first donor robotic hepatectomy (right inferior lobe) was reported by Giulianotti et al. [18]. In a report by Chan et al. (which was the first comparative study between open and robotic donor hepatectomy), 13 patients undergoing robotic donor right hepatectomy were compared with 54 patients undergoing open surgery [19]. There was no conversion, and the two groups had similar blood loss, complication rate and donor liver function recovery. The requirement for postoperative patient-controlled analgesia and period of return to work were lower in the robotic donor group, but operative times were increased. The recipient outcomes had similar early allograft dysfunction (EAD) as defined by the Olthoff criteria [20]—presence of one or more of the following: bilirubin ≥10 mg/dL on day 7, international normalised ratio of >1.6 on day 7 and alanine or aspartate aminotransferases of >2000 IU/L within the first 7 days, complications and 1-year recipient liver function with the open group.

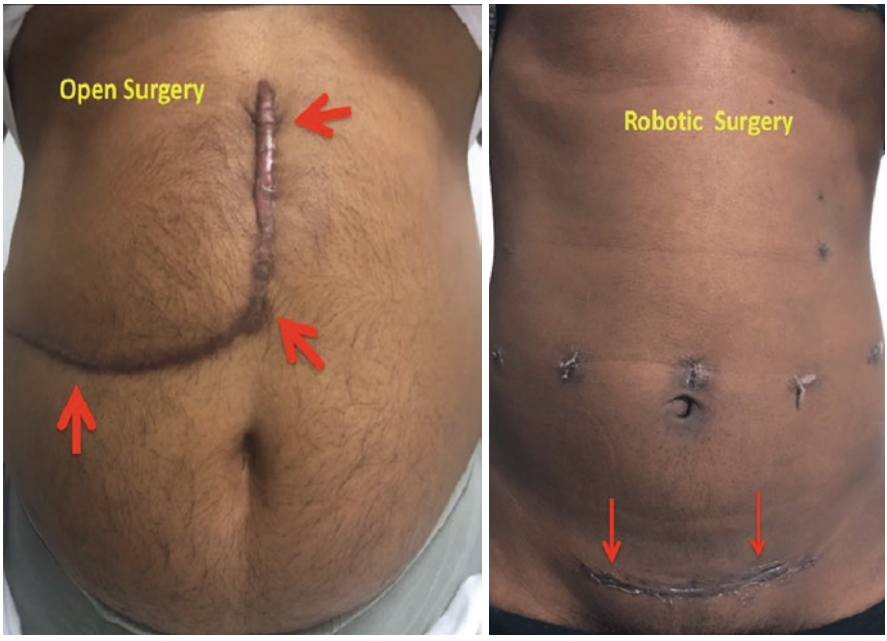

Fig. 7.1 A comparison of scars of robotic and open donor hepatectomy

In the 2018 International Consensus Statement [21], it was recommended that "robotic liver donor hepatectomy is an alternative but should only be performed by experienced surgeons, and the true benefits need further investigation" (level of evidence: very low; level of recommendation: weak, grade 2D). Robotic approaches have their own limitations, which include haptic numbness, difficulty in obtaining operative radiographic cholangiogram, lack of parenchymal transection tools especially CUSA, and delay in undocking in case of emergency conversion. Though few articles have shown comparable results, these outcomes cannot be generalised, and emergency conversion remains a concern in view of the need for undocking and gaining patient access.

7.3 Overview of Technique

Most of our liver grafts have been modified right lobe grafts, where we leave the middle hepatic vein (MHV) with the donor left lobe. A few left hepatectomies or left lateral hepatectomies were done for paediatric recipients. Segment 5 and 8 veins are used to reconstruct the MHV with either dacron/polytetrafluoroethylene (PTFE) graft or the recipient portal vein (Fig. 7.5). All patients taken up for robotic hepatectomy had a preoperative magnetic resonance cholangiopancreatography (MRCP). Our only exclusion criteria for robotic hepatectomy is more than two ducts on MRCP at the level of transection. Indocyanine green (ICG) is given 2 h before induction of anaesthesia so that at the time of bile duct division, the biliary system is highlighted. The patient is kept in reverse Trendelenburg position (25^0 head up) and a right-side elevated position. The Da Vinci Xi system is used (Intuitive Surgical) with bipolar Maryland, monopolar scissors, cadiere forceps, needle holders and Hem-o-lok clip applicator arms for the robotic system. Laparoscopic CUSA, laparoscopic Goldfinger retractor and vascular staplers were used through the assistant port to aid the procedure.

Four 8 mm ports are placed in a transverse straight line along with a 12 mm assistant port. Initial steps include dissection of the falciform up to the groove between the middle and right hepatic veins. This is followed by hilar dissection where the Calot's dissection is performed first after which the cystic artery and duct were identified and divided. Cholecystectomy followed by dissection on the right side of the duct to expose and loop the right hepatic artery and the right portal vein is carried out. Right portal vein and hepatic artery are clamped temporarily to demarcate the plane of division. The right lobe is then mobilised after dividing the right triangular ligament and dividing small veins draining into the inferior vena cava. Placement of sterilised rubber bands sutured onto each lobe helps greatly in graded retraction of the liver lobes during transection. A combination of monopolar scissors and bipolar Maryland forceps is used for initial transection similar to Kellyclysis, and we call it Robotoclysis (Fig. 7.2). Laparoscopic CUSA operated by an experienced assistant through the 12 mm port helps in dissection near the major veins (Fig. 7.2). Veins above 3 mm are clipped using steel or Hem-o-lok® clips.

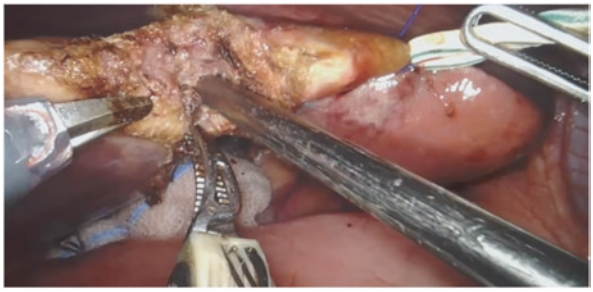

Fig. 7.2 Parenchymal transection with robotic monopolar scissors, bipolar Maryland forceps [Robotoclasia] and lap CUSA through assistant port

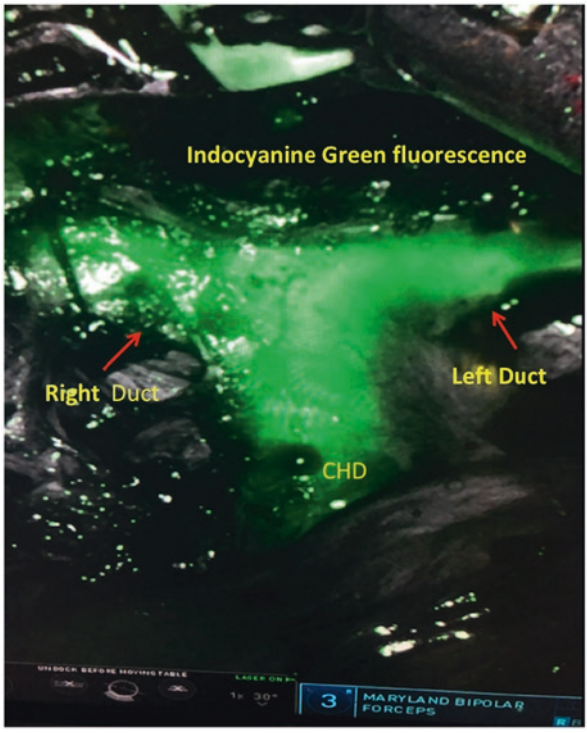

Fig. 7.3 ICG being used to highlight the biliary anatomy

Large veins used for MHV reconstruction are divided with Hem-o-lok clips. Bleeding during transection is controlled with diathermy, fibrillar cellulose or sutures (8 cm, 5-0 Prolene). Parenchymal transection is continued till the transection reaches deeper to the hilar plate level. MHV is usually identified at this plane, looped (8 cm vessel loop) and divided. The duct is divided after division of MHV, and ICG is very useful in delineating the extrahepatic ductal anatomy. ICG is given at the time of induction, approximately 4 h before duct transection to allow it to be excreted into the biliary system from the liver, so as to minimise contamination of the field with the ICG in the liver parenchyma (Fig. 7.3). The duct is divided sharply with robotic scissors, and the donor stump is closed using continuous 6-0 Maxon

suture. This is one area where the precision of the robotic system has a definite advantage over laparoscopic systems. The rest of the hilar plate antero-superior to the portal vein (usually containing minor caudate ducts) is looped along the already divided caudate lobe plane (using 8 cm umbilical tape), clipped with Hem-o-lok® clips on either side and divided. Subsequent parenchymal transection is continued till the anterior aspect of the IVC is fully exposed. A 12–14 cm Pfannenstiel incision is placed and opened up to the peritoneum. The mobilised right lobe is placed in an endobag. The hepatic artery is divided with two Hem-o-lok clips on the donor side, and the portal vein is divided after applying two Hem-o-lok clips on the donor side and one on the graft side (which can be subsequently removed). A white endo-stapler is used to divide the right hepatic vein (Covidien iDrive) and Macuchi (hepato-caval) ligament (Fig. 7.4). The specimen is removed through the Pfannenstiel incision after opening the peritoneum. With practice and proper coordination, the graft retrieval times have significantly improved, but warm ischemia time remains significantly more than open donor hepatectomy. After retrieval, the incision is closed, robot is redocked and after ruling out any bile leak, the left lobe is fixed and the drain is placed along the cut surface of the liver and the ports are closed.

With our experience of more than 220 robotic donor hepatectomies, we would like to indicate some precautions that one should be aware of before attempting robotic donor hepatectomy:

- Haptic numbness: There is no haptic feedback with the robotic system. This can result in liver lacerations or trauma to the graft while applying traction during mobilisation or transection.
- Intraoperative cholangiogram is cumbersome and virtually impossible with a docked robot. Intraoperative biliary anatomy is therefore based mainly on MRCP, and hence a good quality MRCP is essential to avoid surprises intraoperatively. ICG cholangiogram delineates only extrahepatic anatomy. In aberrant biliary anatomy, especially where segment 4, 3 or 2 ducts join the right side, the risk of biliary injury is high.

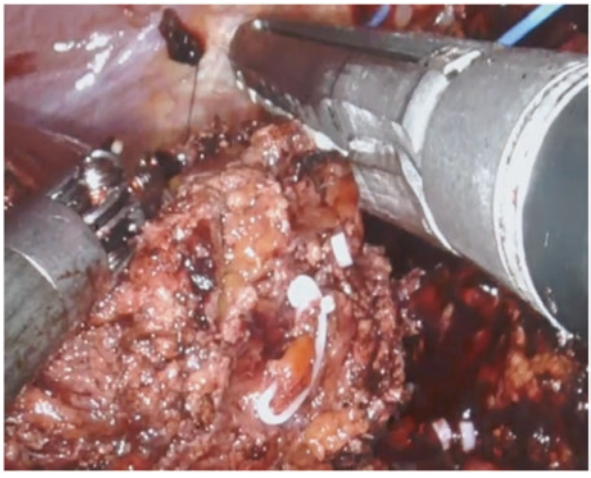

Fig. 7.4 Stapled division of the Right Hepatic Vein [Covidien IDrive]

Fig. 7.5 Liver graft after retrieval

- Bleeding during transection: This is an important concern especially during the final steps of transection and mobilisation of the liver off the inferior vena cava. Whenever venous bleeding occurs, applying compression with a gauze should be the preliminary step. Suction system is crucial. An experienced assistant at the table side is very crucial to use suction not only to show the site of bleeding but for appropriate retraction as well. Increasing positive end expiratory pressure (PEEP) at this point could be dangerous due to the risk of massive air embolism. However, stopping ventilation temporarily to time with the placement of stitches could be helpful for the robotic surgeon to lessen bleeding and enhance vision. An experienced team should be ready by the table side with appropriate instruments to avoid any delay if conversion is required.
- Graft retrieval: It is advisable to complete this carefully with no unnecessary hurried movements. We have found that 15–20 min of warm ischaemia time does not affect the patient or the recipient outcome. At the same time any avoidable delays should be eliminated with adequate preparation prior to clamping the artery and portal vein. A juxtaposition to best describe this would probably be "Hurry slowly"!

The average time for a robotic donor hepatectomy has been 8–14 h compared to 6–8 h for an open donor hepatectomy. Primary warm ischaemia time, which is the time from clamping the hepatic artery to completion of the graft retrieval, has been considerably longer and have averaged 15 min compared to 8 min for an open hepatectomy. Contrary to international findings, our blood loss has been higher in robotic donor hepatectomy compared to open donor hepatectomy (530 ± 223 vs. 390 ± 176). Though we expected the longer duration of surgery to reflect in the immediate

postoperative period, surprisingly we found that the peak bilirubin and peak transaminase elevation post-surgery was significantly lower for the robotic donor group than that for the open donor group (3.06 ± 1.42 vs. 4.09 ± 1.79). One hypothesis for this could be the gentler handling of the liver in robotic surgery than that of an open surgery.

The increased warm ischaemia time, surprisingly, did not have any impact on the recipient either as the recipient laboratory values quantified by peak bilirubin, peak transaminases and peak INR showed no difference in comparison to our open donor hepatectomies. There was no significant difference in the incidence of hepatic artery thrombosis or postoperative blood-borne infections when we compared recipients of robotic and open donor hepatectomies.

Nonetheless, we have seen 4 Clavien Dindo (grade 3) complications among our first 100 robotic donor right hepatectomies. These include biliary injury necessitating hepaticojejunostomy, diaphragmatic hernia requiring repair, portal vein narrowing requiring open repair and IVC narrowing requiring patch repair.

Short-term quality of life (QOL) of donors using SF-36, however, did not show any convincing benefit of robotic right donor hepatectomy over open donor hepatectomy. We are awaiting results of long-term QOL and return to work.

To conclude we would state that robotic donor hepatectomy is feasible, but there is a steep learning curve, with quite a few initial challenges to overcome. However, with the advent of more liver-friendly robotic devices in the future, it may become the new standard of care.

Editorial Comments

Minimally invasive surgery (MIS) has become well established for various procedures. With the advent of robotic surgery, the field of MIS has been expanding rapidly. Improvement in technology and decrease in costs with modern day robot system have made this form of MIS more attractive. The technological advances include better optics, insufflators and various instruments. Robotic surgery (RS) provides better vision, more flexibility of movement of the instruments and eliminates physiological tremors of the surgeon. With these developments, complex operations like liver transplantation can now be done with RS.[1] Its use in contemporary living donor liver transplantation is thus not a surprise! Donor hepatectomy both left and right lobe has been done successfully.[2] The left lobe resection is arguably more favourable for RS than a right lobe one because of ease of dissection, relatively constant anatomy and a much smaller transection line. For a recipient a left lobe graft works as well as a right lobe graft.[3] The advantages of MIS donor hepatectomy are reduced morbidity, shorter hospital stage, early resumption of day to day activity including work and a much smaller wound (wound related morbidity like pain, scar, infection, incisional hernia are the major morbidity of an open operation).

Inspite of these positive developments, RS for liver transplantation has not attracted wide acceptability as one would have expected. This is due to several factors:

1. The results of RS have not been shown to be better than the conventional ones.
2. Though technological advances are occurring, their pace is slow and as a result suitable instruments are still not available (may be a temporary factor!).
3. There is a long learning curve associated with the art and practice of RS in general and donor hepatectomy in particular.
4. Applicability of RS for right lobe grafts (which need extensive mobilization of both the right lobe and the inferior vena cava) is difficult.
5. Concern with the increased warm ischemia time associated with the increased operation time of RS is another factor.

Notwithstanding all these one should welcome this new form of surgery for better management as long as this is done by experienced surgeons (already gone through the learning curve) in dedicated centres specializing in this field.

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Chapter 8
Assessment of Tumour Response to Neoadjuvant Therapy for the Treatment of Oesophageal Cancer

Carlos S. Cabalag, Jonathan Sivakumar, and Cuong P. Duong

8.1 Introduction

Multi-modal therapy with neoadjuvant chemotherapy or chemoradiotherapy (CRT) followed by surgery is the standard of care for resectable locally advanced oesophageal cancer (OC) as it has been shown to improve patient survival when compared with surgery alone [1]. The potential advantages of neoadjuvant therapy include downstaging of the primary tumour to facilitate resection with clear margins and to treat systemic micro-metastatic disease [2].

Assessment of tumour response to neoadjuvant therapy is important. Identifying patients who develop incurable metastatic disease avoids futile surgery. Conversely, pre-operative chemotherapy or CRT can induce pathological complete response (pCR) in 16–23% of oesophageal adenocarcinoma (OAC) and 49% of oesophageal squamous cell carcinoma (OSCC) [3]. As pCR confers significant 5-year survival benefit [4], the ability to predict pCR may alter the treatment paradigm to a 'watch-and-wait' approach for the patients with equivocal surgical fitness. The current SANO trial [5] will evaluate whether OC patients who achieved clinical complete tumour response following CRT can have active surveillance rather than routine oesophagectomy.

This chapter discusses the efficacy of current available techniques as well as pre-clinical biomarkers in assessing response following neoadjuvant therapy for OC.

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8.2 Current Methods of Assessing Response

8.2.1 Gastroscopy and Endoscopic Ultrasound

Gastroscopy: Whilst gastroscopy and biopsy is the standard initial method to establish tissue diagnosis of OC, it has a limited role in assessing tumour response following neoadjuvant therapy. A meta-analysis from Van Rossum et al. evaluated the role of endoscopic biopsy for determining residual OC after CRT [6]. Based on the findings of 12 studies consisting of 1281 patients, where a positive biopsy was considered 'ypT+', endoscopic biopsy was found to have good specificity (91.0%) but poor sensitivity (34.5%). Whilst the endoscopist's experience is important, chemoradiation-induced inflammation increases sampling errors and false-negative biopsy rates [7]. Furthermore, superficial biopsies cannot account for the presence of deeper residual tumours that are not apparent on the mucosa.

A recent prospective multicentre study by Noordman et al. (pre-SANO trial) [5] investigated whether taking two consecutive biopsy samples from the same site, termed a 'bite-on-bite' biopsy, increases the accuracy of detecting residual submucosal disease (Fig. 8.1). This was performed in conjunction with a fine-needle aspiration (FNA) of suspicious lymph nodes. When compared with the standard biopsy technique, the bite-on-bite approach was more accurate with superior sensitivity (74.0% vs 54.0%) and specificity (77.0% vs 69.0%) and a positive predictive value of 92.0%. Other smaller studies have also demonstrated improved accuracy of the 'bite-on-bite' method [4, 8, 9]. However, given the sub-optimal sensitivity, a negative endoscopic biopsy result alone cannot exclude residual tumour following neoadjuvant therapy.

Endoscopic ultrasound (EUS) and fine-needle aspiration (FNA): EUS utilises a high-frequency ultrasound transducer to assess tumour thickness and cross-sectional

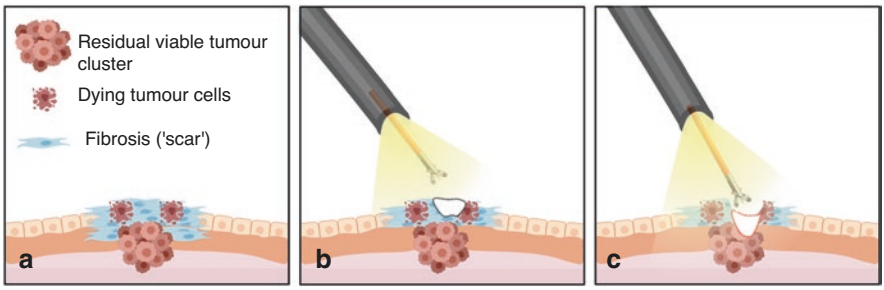

Fig. 8.1 'Bite on bite biopsy'—(**a**) In patients who respond to neoadjuvant chemoradiation, the primary tumour reduces in size. As tumour cells die, a number of tumour cell clusters may still survive and invade deeper layers such as the submucosa or muscularis propria. (**b**) A single biopsy may only obtain a superficial area of fibrosis and dying tumour cells, possibly missing a deeper area of viable tumour. (**c**) By taking a second deeper biopsy at the same site, the probability of detecting residual disease increases (Image created with Biorender.com)

area, as well as the depth of tumour invasion [10]. Sonographic features suggestive of a malignant lymph node (rounded shape, clear borders, uniform central hypoechogenicity and short-axis diameter >10 mm) can guide FNA sampling to ascertain tissue diagnosis [11].

While EUS is considered the most accurate method for assessing the initial T staging (depth of tumour infiltration) of OC, it has questionable accuracy following CRT in predicting cancer regression or remission [12]. Like other structural imaging modality, EUS cannot reliably distinguish inflamed oesophageal tissue from tumour. The meta-analysis from Van Rossum et al. compared post-neoadjuvant EUS findings with histopathological result of resected OC specimens [6]. This included 11 studies (593 patients) reporting on ypT status and ten studies (602 patients) reporting on ypN status. EUS has high sensitivity (96.5%) but very low specificity (10.9%) in assessing residual primary tumour. It is better at evaluating malignant lymph nodes (LN) with sensitivity and specificity of 62.0% and 56.7%, respectively. Vazquez-Sequeiros et al. showed that the addition of FNA to EUS can improve the accuracy of detecting residual LN metastasis [13].

The utility of EUS is restricted in the setting of tight malignant oesophageal strictures due to inability to pass the endoscope and the risk of perforation [10]. Another consideration with the use of EUS is that it is operator-dependent and prone to significant interobserver variation. Thus, it is recommended for EUS to be performed by experienced investigators at high-volume institutions [10].

8.2.2 Structural Imaging (CT and MRI)

The Response Evaluation Criteria in Solid Tumours (RECIST) criteria, originally published in 2000 and later revised in 2009 [14, 15], are widely accepted for assessing the radiological response of CRT. These were developed against the gold-standard histological assessment of resected tumour and LN specimens. The revised RECIST guidelines classify treatment status as a complete response, partial response, progressive disease or stable disease (Table 8.1).

Computed tomography (CT): Due to easy accessibility, CT scan is commonly used for the initial staging of OC and in the assessment of tumour response to neoadjuvant therapy. It is most useful for excluding distant metastasis, which would alter treatment intent and avoid futile surgery. With regard to the primary OC, CT provides valuable information about tumour morphology, dimension and volumetry. The accuracy of CT for assessing tumour response in OC patients following neoadjuvant treatment (NAT) has been analysed in a meta-analysis of eight studies (471 patients) by de Gouw et al. [16] All studies adopted a volume-based criterion to define therapeutic response. The pooled sensitivity and specificity for CT scan in predicting a complete response in the primary tumour (ypT0) were 68.0% and 96.0% and of draining LN (ypN0) were 79.0% and 45.0%, respectively.

Table 8.1 RECIST criteria

Response category	Criteria
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10 mm
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (Note: Appearance of one or more new lesions is also considered progression)
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Adapted from: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). Eur J Cancer (2009) 45(2):228–47

With the move from single-slice scans towards multi-detector scans, the accuracy of CT scan to assess tumour response has improved as a result of thin sections and multiplanar reformation tools [17]. CT can assist in determining resectability of OC if there is relative preservation of fat planes between the tumour and adjacent structures of the mediastinum [18]. However, there is limit in CT resolution so that it cannot differentiate between viable residual tumour and reactive change from neoadjuvant therapy [11].

Magnetic resonance imaging (MRI): Given its excellent soft tissue contrast and resolution, MRI has gained increased attention as an advanced imaging technique to assess treatment response. This imaging modality has been investigated in oncology primarily as a diffusion-weighted (DW) sequence or dynamic contrast-enhanced (DCE) sequence. DW-MRI measures the apparent diffusion coefficient (ADC), that being the diffusion rate of water molecules within a tissue [19]. As diffusion within a tumour is restricted to cellular membranes and other corresponding structures, ADC is an indicator of cellularity and subsequently is decreased in the presence of cancer [20]. As a result, ADC is expected to increase in the setting treatment response. DCE-MRI is undertaken with fast T1-weighted spoiled gradient echo sequences and evaluates the movement of gadolinium contrast to calculate tumour perfusion. This permits assessment of the area under the gadolinium curve or from calculating the signal intensity through biophysical modelling [11].

De Gouw et al. evaluated three prospective studies on the predictive value of MRI restaging for histopathological response. These studies defined complete tumour response as an ADC difference >40.0% in DWI MRI or an AUC difference >24.6% in DCE MRI. The sensitivity and specificity of MRI for predicting pathological complete response (ypT0) was 80.0% and 83.0%, respectively [16]. Whilst the results of this analysis are promising, the utility of MRI in assessing treatment response in OC is not routine due to its limited availability within the community.

8.2.3 *Functional Imaging*

Position emission tomography (PET): Most OC can be visualised on PET scan as they have higher avidity to the radiolabelled agent ^{18}F-fluorodeoxyglucose (18F-FDG) than normal tissue. Hence, PET can assess treatment response by evaluating the change in metabolic uptake of 18F-FDG using various parameters including visual assessment of metabolic tumour volume, total lesion glycolysis and standardised uptake value (SUV) (Fig. 8.2). The PET Response Criteria in Solid Tumours (PERCIST), adapted from the RECIST criteria, were developed as a standard for assessing tumour response based on SUV normalised for lean body mass (SUL) [21, 22]. This categorises patients into one of four groups—complete metabolic response, partial metabolic response, stable metabolic disease and progressive metabolic disease (Table 8.2).

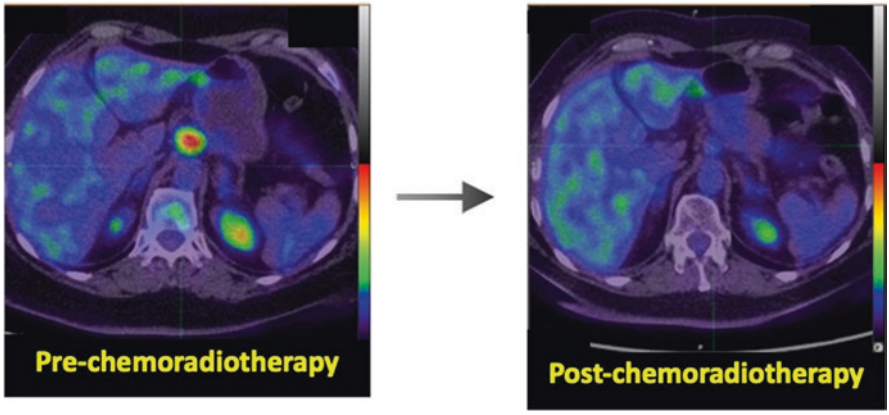

Fig. 8.2 Utility of post-neoadjuvant treatment restaging 18F-FDG PET scan. This patient underwent CROSS protocol neoadjuvant chemoradiation. Baseline PET scan images on the left compared to restaging PET scan 4 weeks following completion of neoadjuvant treatment demonstrates a complete metabolic response of the tumour

Table 8.2 PERCIST criteria

Response category	Criteria
Complete metabolic response	Visual disappearance of all metabolically active tumour
Partial metabolic response	>30% decrease in SUL peak (minimum 0.8-unit decrease) in lesion with greatest uptake (not necessarily in same lesion)
Progressive metabolic disease	>30% increase in SUL peak (minimum 0.8-unit increase) >75% increase in total glycolysis Confirmed new lesions
Stable metabolic disease	Does not meet other criteria

Adapted from: Wahl R.L., Jacene H., Kasamon Y., Lodge M.A. From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors. J. Nucl. Med. 2009;50(Suppl. 1):122S–150S

A systematic review of 13 studies showed 18F-FDG PET to be a good tool for the assessment of tumour response [23]. However, the definition of PET metabolic response varied between studies and was largely based on either a 30%–35% reduction in SUVmax or on an absolute threshold of SUVmax <2.5 on post-treatment imaging. The reported sensitivity and specificity for predicting pathological response was 70.3% and 70.1%, respectively. One limitation of PET metabolic imaging is that radiation-induced oesophagitis has high FDG uptake that may be indistinguishable from residual tumour [24]. The diagnostic accuracy of 18F-FDG PET may also be adversely influenced by factors such as patient size, plasma glucose concentration and respiratory motion artefact [25, 26].

Whilst there is currently no consensus regarding the optimal time period at which to assess treatment response, the majority of studies in the literature have performed restaging PET at 4 to 6 weeks following the completion of neoadjuvant therapy. As biochemical changes in a malignancy following NAT precede a change in tumour size, PET can also be used to detect early treatment response [27]. The identification of OC patients whose tumours are not responding allows changes in treatment algorithms as demonstrated in the MUNICON I and MUNICON II trials [28, 29]. PET was performed at 14 days after the commencement of neoadjuvant chemotherapy. Responders who achieved a tumour reduction in SUVmax ≥35% continued with chemotherapy prior to tumour resection, whilst the nonresponders either proceeded straight to surgery (MUNICON I) or changed to CRT then surgery (MUNICON II). The MUNICON trials demonstrate the utility of early PET assessment in tailoring neoadjuvant treatment, with the finding that the addition of CRT in nonresponders did not significantly increase overall survival compared to chemotherapy and surgery. Moreover, the limitations of early PET assessment in the neoadjuvant setting include the lack of an agreed SUV cut-off value that differentiates a responder from a nonresponder, and the likelihood of false-positive results in the assessment due to the local inflammatory effects of CRT. For these reasons, early treatment response assessment with PET is currently not recommended as standard practice.

Another important role of restaging PET is the detection of interval or distant metastases, which can develop in 8–17% of OC patients undergoing neoadjuvant therapy [24–26]. PET can also provide prognostic information with a reduction in tumour SUVmax ≥35% to be predictive for long-term survival [29].

The advent of hybrid PET-CT has integrated the higher-resolution anatomical detail into PET imaging, to improve the diagnostic accuracy and interpretation of many lesions. Like PET imaging, PET-CT carries an important role for identifying interval metastases on restaging scans [30], although there is a paucity of literature to compare these tools following chemotherapy [31]. Particularly in the detection of liver metastases, PET-CT has been found to be superior in the early detection of liver lesions compared with PET alone [32, 33]. Furthermore, trials have demonstrated that the adoption of PET-CT has altered management in 20%–30% of cases [34–36]. In light of its superior accuracy in this setting, mounting evidence supports the central role of PET-CT as the preferred functional imaging in the assessment of treatment response.

8.3 Pathological Assessment of Resected Tumour Post-Neoadjuvant Treatment (yp Staging)

Tumour regression grading (TRG) systems were created to categorically characterise the amount of residual tumour from fibro-inflammatory tissue (scar) induced by NAT. The standard in reporting histopathological response to neoadjuvant therapy in OC, termed 'yp' staging, was established by Mandard et al. [37]. The Mandard TRG is a categorical 5-point grading system whereby TRG 1 represents a complete pathological response and TRG 5 signifies no histological evidence of tumour response to CRT (Fig. 8.3). This study of 93 resected specimens (83% OSCC) was conducted to determine if tumour regression post-neoadjuvant CRT was associated with disease-free survival. On multivariate analysis, only TRG (TRG 1–3 versus TRG 4–5) was a significant independent prognostic factor of disease-free survival. More recent work by Noble et al. confirmed these findings by Mandard in a multicentre cohort study, as well as the finding that LN downstaging from neoadjuvant chemotherapy was associated with improved overall survival [38]. Although the TRG grading systems have no impact on altering the course of treatment preoperatively, numerous studies have shown a role in its ability to prognosticate.

Despite a number of studies suggesting that TRG is an independent prognostic factor, it has its limitations. Firstly, histopathological examination is prone to inter and intra-observer variability. Moreover, this potential variability is reflected in the fact that there is no single, widely accepted TRG classification system for OC, with nine different systems of grading internationally [39]. Most importantly, the current TRG classification systems do not account for the status of nodal metastases post NAT termed 'ypN'. To illustrate the significance of nodal metastases, the main findings from a large worldwide series of neoadjuvant pathological staging data reveal that persistence of nodal metastatic disease post-NAT portends poor survival irrespective of 'ypT' status [40]. Another problem in the assessment of tumour regression is the lack of standardisation in sampling surgical specimens, which is especially important for categorising a response as pCR—ideally the entire tumour site should be histologically examined.

8.4 Novel Methods of Assessment

Pre-existing methods to assess the response to NAT have largely been imaging based and are limited by the nature of the technology used as well as inter-operator variability. More sensitive and objective methods in the areas of molecular-based biomarkers, circulating tumour cells and circulating tumour DNA are currently in development. The improvement in overall survival for OC not only depends upon the development of novel therapeutic strategies but is also incumbent upon sensitive and accurate noninvasive methods to assess for treatment response in the pursuit of optimising patient management.

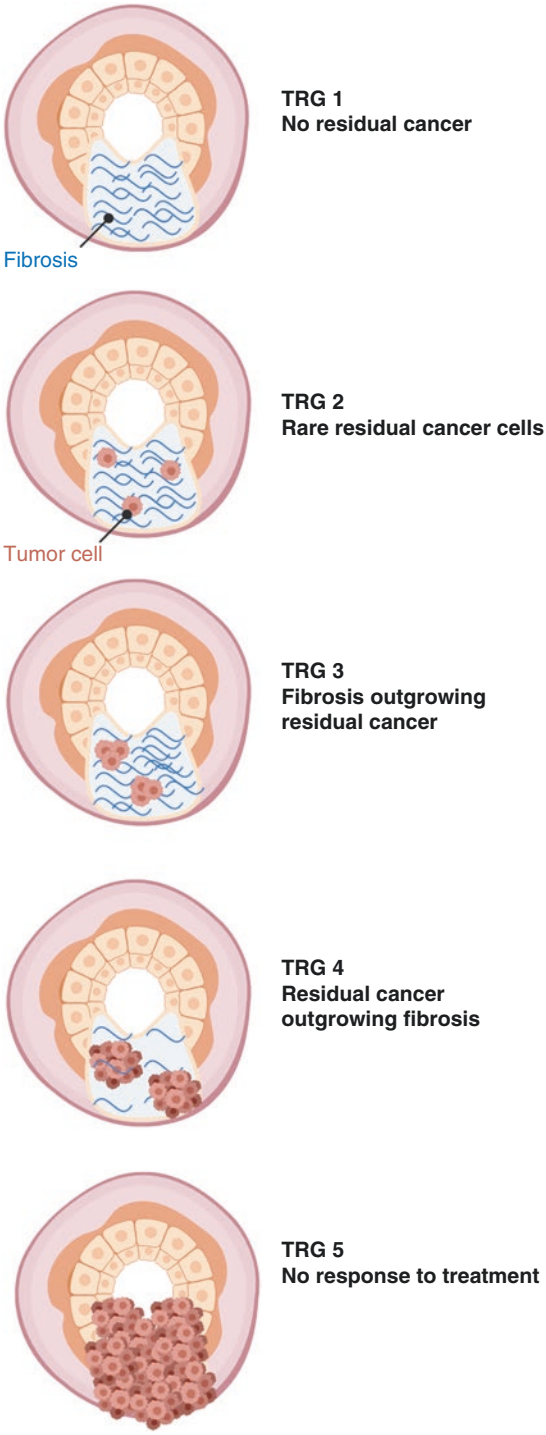

Fig. 8.3 Tumour regression grade (TRG) for post-neoadjuvant treated oesophageal cancer according to Mandard et al. Each tumour grade is depicted by a cross section of the oesophagus that is a representation of the histological features. In TRG 5, an absence of fibrosis with tumour growth indicates no response to treatment (Image created with Biorender.com)

8.4.1 Molecular-Based Biomarkers

The search for a clinically informative biomarker in OC is challenging owing to the genetic diversity of the tumour type [41–43]. A patient may harbour a combination of genetic mutations that are differentially regulated by epigenetic mechanisms, which are unique from a patient-to-patient basis. For these main reasons, there has not been a widely adopted molecular biomarker for OC that has been utilised in the clinical setting.

Carcinoembryonic antigen (CEA) is a well-recognised tumour marker that first demonstrated its clinical utility in the detection of early recurrent disease for colorectal cancer [44]. For OSCC, elevated pre-treatment CEA levels were associated with a lower rate of pCR [45] and a significantly worse median time to disease recurrence and overall survival [46]. To date, two studies have examined the change in CEA levels following neoadjuvant therapy with conflicting results. In one study, CEA levels measured at 3–6 months following surgery and neoadjuvant CRT remained elevated in 83% of patients, although there was no correlation between CEA levels with survival [47]. On the contrary, Kim et al. [48] reported a decrease in the number of CEA-positive patients (22.2–10.9%) following chemotherapy, with those who remained CEA positive having worse disease-free survival.

TP53 is the most commonly mutated gene in both OAC and OSCC affecting approximately 70% of the cohort [49]. Its primary function as a tumour suppressor serves to maintain cellular homeostasis through the coordination of a complex framework of molecular pathways [50]. The generation of an abnormal mutant p53 protein triggers the host immune system to synthesize specific anti-p53 antibodies. This antibody can be measured in the patient's serum in a number of malignancies including OC [51].

Cai and colleagues [52] investigated the change in serum levels of anti-p53-Ab before and after radiotherapy in patients with OSCC. For patients who were p53-Ab negative, 72% had a partial or complete tumour response. In comparison, all patients who had no response to radiation were p53-Ab positive post-treatment. The study by Yamashita [53] examined the effect of neoadjuvant chemotherapy on serum p53-Ab. Although there was no significant correlation between pre- and post-treatment serum antibody titres and tumour response, an increase in serum p53-Ab titres post-neoadjuvant chemotherapy was independently associated with a shorter recurrence-free survival. The caveat with measuring serum p53-Abs is the supposition that the patient will mount an immune response against the tumour to generate detectable antibodies. Emerging studies exploring the tumour immune microenvironment in OC reveal that only 36% of tumours are immunologically responsive (46% in OAC and 18% in OSCC) [54] thus likely explaining the inter-patient variability in serum p53-Ab positivity.

8.4.2 Circulating Tumour Cells

Circulating tumour cells (CTC) are released from the primary tumour mass due to its predisposition for metastasis. The earliest work on CTC can be traced back to 1869 where a Melbourne hospital resident physician by the name of Thomas Ashworth discovered the existence of cells in the blood that were 'identical with those of the cancer' in a post-mortem examination of a patient [45]. Since then, there have been significant improvements in the detection of CTC in order to improve pre-treatment staging and as a biomarker for treatment response.

In the review article by Hoeppner et al. (mainly in OSCC), the persistence of CTCs in the follow-up samples of patients after definitive CRT and/or surgical resection appeared to be predictive of shorter disease-specific survival [55]. In the setting of OAC, Pernot et al. showed that patients with decreased CTC counts post treatment had higher progression-free survival than those with increased CTC count, 8.9 months versus 2.9 months [56].

Future work on CTC will combine assays that detect ctDNA as well as specific cell surface receptors that are more specific for CTCs that are responsible for metastatic seeding.

8.4.3 Circulating Tumour DNA (ctDNA)

DNA from tumour cells is released into the circulation either from necrotic and apoptotic cells or through active secretion via exosomes [46] (Fig. 8.4). Through analysis of the patient's blood sample, ctDNA can be identified by the presence of tumour-specific, somatic mutations and quantified by using PCR-based assays and next-generation sequencing techniques [57].

Emerging evidence suggest that the levels of ctDNA can be used in monitoring treatment response and in the detection of disease recurrence in various cancer types [58, 59]. The study by Egyud et al. [60] shows how ctDNA levels can be used as a dynamic biomarker to monitor the patient's response to NAT. A decrease in ctDNA levels post NAT in one patient correlated with their partial response on restaging PET. Conversely, a rise in ctDNA levels during NAT correlated to another patient's progressive peritoneal disease confirmed on restaging PET-CT. Similarly, Ueda et al. [61] monitored ctDNA levels in four cases also showing that ctDNA VAF is a potentially sensitive marker that is reflective of patient tumour burden.

Furthermore, ctDNA in combination with PET may also predict patients who might be at higher risk of disease progression. Azad et al. demonstrated that the presence of ctDNA and a decrease in tumour volume below a certain threshold as measured by PET confer a significantly higher risk of disease progression [62]. In addition to this, the emergence of new somatic mutations in ctDNA post NAT may be associated with disease progression.

Future studies will need to focus on elucidating the kinetics of ctDNA during NAT and how it compares to established methods of assessing response such as PET-CT and histopathological tumour regression grade.

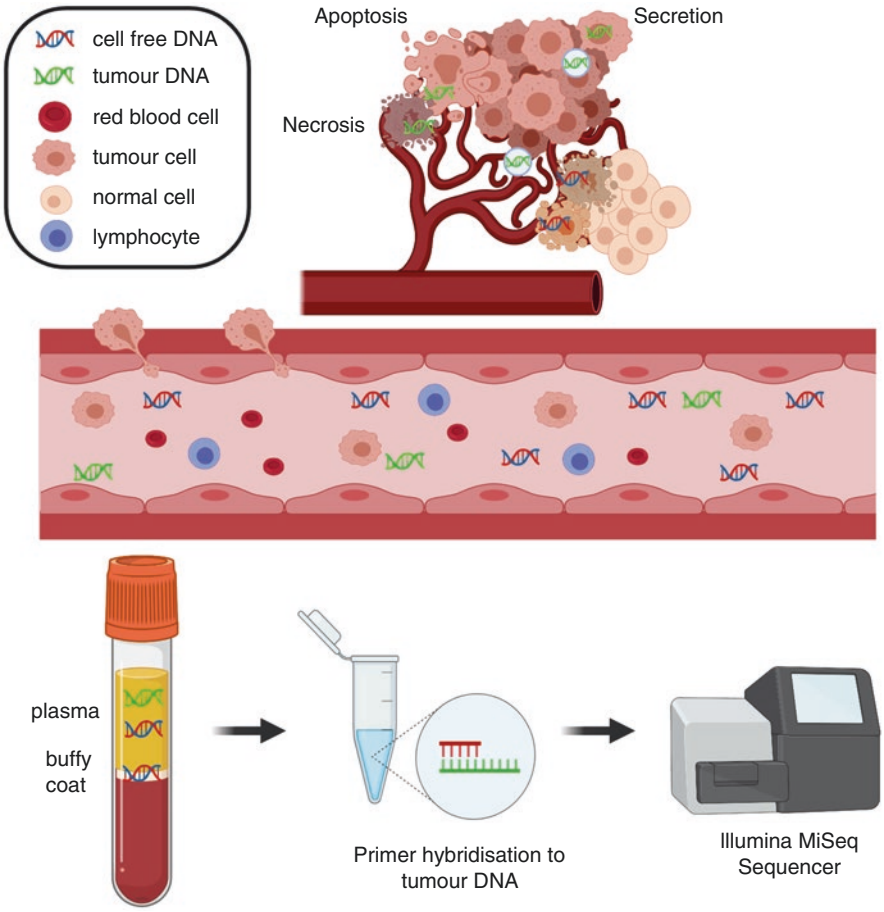

Fig. 8.4 Process of measuring the presence of circulating tumour DNA (ctDNA). ctDNA and normal cell-free DNA are released via cellular apoptosis, necrosis or active secretion in exosomes. DNA fragments from plasma or serum are isolated and incubated with mutation-specific primers. The abundance of tumour-specific mutations are measured through sequencing (Image created with Biorender.com)

8.5 Conclusion

A multimodality therapeutic approach with chemotherapy or CRT followed by surgery is the main curative treatment for locally advanced OC. However, the majority of patients (77% of OAC and 51% of OSCC in CROSS trial) do not achieve pCR, whilst some OC patients develop interval metastatic disease. Hence, accurate assessment of tumour response to neoadjuvant therapy allows individualised treatment selection. Therapy can be changed for nonresponders, and those with disease progression will avoid futile surgery.

Restaging 18F-FDG PET, with or without CT, is the best current noninvasive method of detecting of interval distant metastases. Accurate assessment of complete

response at site of primary OC is challenging due the inflammatory response caused by neoadjuvant radiotherapy and the technical limitations of available endoscopic and imaging modalities. 'Bite-on-bite' endoscopic biopsy increases the yield of detecting residual tumour but a negative biopsy does not equate to a complete response. Further research is required to evaluate the role of MRI in assessing treatment response for OC.

The ideal biomarker(s) in OC can dynamically monitor tumour response and provide prognostic information that can impact on treatment decision making. Insufficient sensitivity and the lack of a clinically valid 'cut-off value' for biomarker response are the main problems inherent in past and current studies. Moreover, the likelihood of a single biomarker being independently prognostic of treatment response and survival is unlikely. The creation of a scoring system combining parameters from different modalities (endoscopic, radiological, pathological, and molecular based) may be one approach in developing a clinically useful test to assess treatment response in OC patients.

Editorial Comments

Neoadjuvant chemoradiotherapy (NCRT) is a well-established form of treatment for resectable oesophageal cancer. It provides complete pathological response in 23% of adenocarcinomas and 49% of squamous cell carcinomas.[1,2] Obviously, these patients with pathological complete response could have been spared surgical treatment. However, in the absence of any post NCRT assessment strategy, this needs to be done in the best interest of the patient. Understandably, those with evidence of a tumour in the primary site or in the lymph nodes should go for surgery, but those without evidence of the same should ideally be spared of an unnecessary and potentially hazardous operation. This situation has brought in the concept of active surveillance strategy to select patients who should and who should not undergo resection. Various tools are used for post NCRT assessment of response as elaborated by the authors. Using PET CT, oesophagoscopy with bite-on-bite biopsy and EUS FNA, Noordman et al.[3] showed the presence of residual disease following NCRT. Whether this is true for oesophageal squamous cell carcinoma also is not known. To answer this, a multicentre study has been initiated (preSINO trial) by Zhang et al.[4] The authors propose to select patients with squamous cell carcinoma and give them NC NCRT. After 4–6 weeks of treatment, the patients will undergo clinical response evaluation 1 (CRE 1). If there is no evidence of tumour on CRE1, patients will continue to receive NCRT and will undergo CRE 2 after 10–12 weeks. If still there is no evidence of tumour, the patients will undergo oesophagectomy. All such patients will be followed up as a part of a subsequent study (SINO trial), which is aimed to compare the results of active surveillance versus oesophagectomy.

To our knowledge, this is only one of its kind of study to address the issue of objective assessment of response to NCRT with clinical utility, i.e. deferring surgery for the complete responders and subjecting the non-responders to oesophagectomy.

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Chapter 9
Proton Beam Therapy in Gastrointestinal Cancers: A Paradigm Shift in Radiotherapy

Ashwathy Susan Mathew and Sapna Nangia

9.1 Introduction

Gastrointestinal (GI) cancers account for around 30% of new cancers among males worldwide and around 17% of the new cancers among females while accounting for around 30% of the cancer deaths in 2018 [1]. Radiotherapy has been playing an increasing role in GI malignancies over the past decades, whether it is definitive radiotherapy in anal canal cancers or neoadjuvant chemoradiation in locally advanced rectal cancers and oesophageal cancers. Techniques of irradiation have been improving too over the same time from two-dimensional techniques using X-rays for guidance to three-dimensional conformal techniques utilising computed tomography (CT) imaging for planning and imaging to intensity-modulated radiation therapy (IMRT) in the beginning of the 2000's. The newest therapy to be clinically available in the armamentarium of radiation therapy techniques is proton beam therapy, the first and currently the only facility in India being located in Chennai.

9.2 Background

9.2.1 Overview of Role of Radiation in Gastrointestinal Cancers

While surgery continues to be the primary modality in curative treatments for a variety of gastrointestinal cancers, radiation therapy is increasingly becoming a valuable tool in the multidisciplinary management of such cancers. Multiple

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randomised trials have established radiation with or without chemotherapy in the neoadjuvant and adjuvant therapy of locally advanced oesophageal and gastro-oesophageal cancers [2], gastric cancers [3] and rectal cancers [4]. Chemoradiotherapy is also established as a definitive therapy modality for unresectable oesophageal cancers [5], unresectable pancreatic cancer [6] and in all but very early stages of anal canal cancer [7]. Radiation therapy is also used in a non-curative context in hepatocellular cancer, liver metastases and cholangiocarcinomas with emerging evidence of substantial, durable local control benefit. Palliative radiation therapy has also long been used to ease cancer pain, provide relief of bleeding and temporarily palliate obstructive symptoms.

The challenge with delivering radiation therapy in gastrointestinal cancers is to deliver high tumouricidal doses to tumours, which are adjacent to luminal organs, which are exquisitely radiosensitive. The consequences of such unintended "spill-over" of radiation onto normal bowel may range from an increased risk of diarrhoea and cramps, to treatment interruption, bleeding, ulceration, stricture, obstruction and, rarely, perforation. Several techniques have been utilised in the past to improve the therapeutic ratio (Fig. 9.1) (a ratio of tumour control probability to normal tissue complication probability), which is particularly narrow in abdominal organs being treated with radiation. Proton beam therapy is a technological innovation in this direction, which is able to reduce doses to normal tissues to a further extent than possible by the most advanced photon irradiation techniques such as volumetric-modulated arc therapy (VMAT) or intensity-modulated radiation therapy (IMRT).

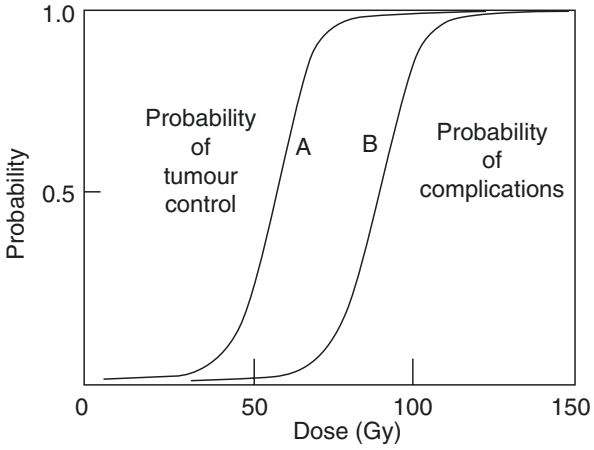

Fig. 9.1 The principle of therapeutic ratio. Curve A represents the tumour control probability (TCP), curve B the probability of complications in normal tissues (NTCP). The total clinical dose is usually delivered in 2 Gy fractions. Optimal dose is one that maximises TCP while minimising NTCP. Reproduced from [8]. Reprinted with permission from the International Atomic Energy Agency (IAEA). Copyright IAEA, Vienna

9.2.2 *Physics and Rationale for Proton Therapy in GI Cancers*

Proton beam therapy (PBT) is a technique of radiation utilising positively charged particles (protons) for delivering radiation to tumours. Protons have a definite mass and charge, unlike X-rays or photons. Due to these physical characteristics, they have unique properties of dose deposition in which the entrance dose is lower than that for photons and the proton deposits the maximum dose at a particular depth within the tissue, after which it stops and dose falls down to zero. This phenomenon is called Bragg peak (Fig. 9.2) in a pristine pencil beam of protons. Effectively this translates into almost zero exit dose for clinical treatments (when using a single beam). Biologically, protons are more or less similar to photons except at the end of the range, where they are postulated to have a higher ratio. This is quantified by the radiobiological effectiveness (RBE), which is estimated to be 1.1 approximately (for reference, photons/X-rays have RBE of 1). Two main kinds of techniques have been used for delivering proton beams, passive scattering and active scanning. In passive scattering, which is the older technique, a uniform beam of protons is shaped to the lateral and distal dimensions of the tumour by patient-specific accessories, which are quite labour-intensive and cumbersome to make and use daily. In active scanning, the pencil beam of protons is directed by magnets, which scan it across the tumour and by modulating the energy of the proton we can "paint the tumour" with the required dose to the tumour layer by layer (Fig. 9.3). Most of the older machines also had only orthogonal X-rays as image guidance, but newer machines have cone-beam CTs similar to those available on modern photon therapy machine (linear accelerators).

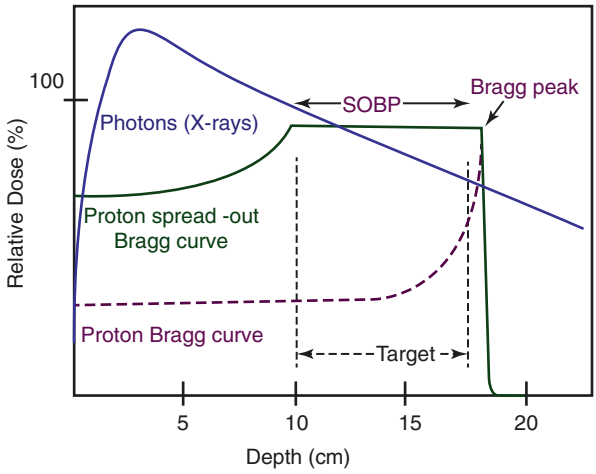

Fig. 9.2 Dose-depth characteristics of pristine proton beam, spread out Bragg peak and photon beam

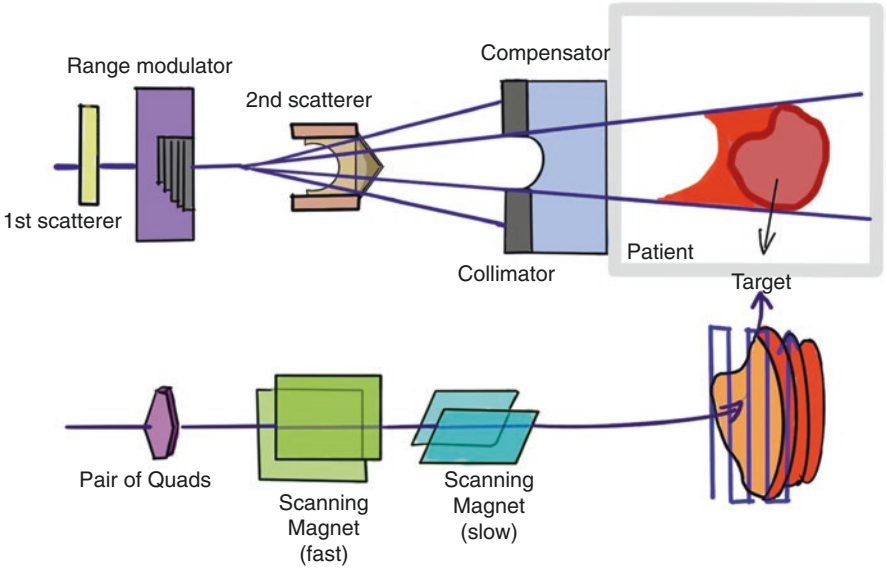

Fig. 9.3 Proton beam delivery techniques: Passive scattering and active pencil-beam scanning techniques

9.3 Role of Proton Beam Therapy (PBT) in Oesophageal and Stomach Cancers

Radiation has two main curative roles in oesophageal cancer: preoperative and definitive. In both the settings, evidence is available that IMRT or VMAT is dosimetrically superior to older 3-D conformal techniques in reducing radiation doses to normal organs adjacent to the oesophagus such as lungs and heart, although there are no randomised controlled trials to support this [9, 10]. In the preoperative setting, this helps to reduce postoperative morbidity and mortality due to pneumonia, atelectasis, pleural effusion, pulmonary embolus, acute respiratory failure and cardiac complications such as arrhythmia, myocardial infarction and left ventricular failure, which is <10% in modern series of IMRT [11]. There is evidence that mean lung doses are correlated with pulmonary complications [12]. In the definitive setting, more concern lies with late toxicity from chemoradiation involving lung and cardiac morbidity/mortality and "other deaths". However, even with VMAT, a larger proportion of the body receives low doses (at least 5 Gy) compared to IMRT and 3-DCRT [13].

Several dosimetric studies have documented that the use of PBT reduces the low to intermediate doses deposited in the heart and lungs, especially in mid-thoracic and GE junction tumours [14]. Specifically intensity-modulated proton therapy has been demonstrated to deliver statistically significantly lower mean liver, lung and heart doses compared with volumetric modulated arc therapy (VMAT) [12].

In large retrospective studies, the use of proton therapy has been found to be associated with shorter hospital stay and lesser pulmonary and wound complications after surgery (16% vs 25% and 5% vs 14%) when compared to photons [15, 16]. The reduction in doses to adjacent normal organs in oesophageal cancer patients has also been shown to be clinically relevant in a prospective randomised Phase 2B trial from the MD Anderson Cancer Centre, which has demonstrated in 145 patients randomised to IMRT vs PBT, that IMRT patients had a higher total toxicity burden when compared to patients treated with PBT, with mean post-operative complication severity score that was 7 times higher [19.2 (7.6–32.7) vs. 2.4 (0.34–5.02)] than with PBT [17]. With median follow-up time of 52.9 weeks, PFS was comparable among both cohorts. Studies from the Mayo Clinic also corroborate this by showing less decline in quality-of-life scores after PBT compared to photon-based radiation therapy, in patients undergoing chemoradiation with neoadjuvant or definitive intent [18].

In squamous cell carcinomas, which are being treated with definitive intent, researchers from Japan have published multiple series where they have investigated the use of proton therapy alone with some dose escalation. These series report high toxicity rates, and some of the reasons attributed to this are the use of radiation alone in higher doses than 50.4 Gy as well as the use of passive scattering techniques.

Future Directions: A randomised trial is ongoing (NRG-GI006) comparing protons to photons in stage I–IVA, excluding T4 oesophageal cancer [19]. Another trial is attempting dose escalation using protons in the neoadjuvant setting [20].

9.4 Role of PBT in Hepatocellular Cancer

Currently, stereotactic body radiotherapy (SBRT) using photon is one of the treatment options for unresectable hepatocellular carcinoma with or without vascular invasion, as well as HCC refractory to or recurrent after other liver-directed therapies. The Phase 1/2 trial from the Princess Margaret Cancer Centre group demonstrated an 87% 1-year local control rate and 50% 1-year OS rate in spite of having large tumours and many of them having macrovascular invasion [21]. The physical properties of protons are the basis of their use in hepatocellular carcinoma, and their lack of an exit dose is particularly advantageous in a cirrhotic liver whose function is compromised at baseline and by prior liver-directed therapies such as RFA, TACE and TARE. Also since the cirrhotic process is progressive and since retreatment might be necessary in the future for recurrences outside the irradiated liver, protons are advantageous because its liver-sparing properties give a greater leeway when considering re-irradiation.

PBT for HCC began in the 1980s in Japan with initial reports showing promising results [22] with 5-year survival and local control rates of 23.5% and 87%, respectively [23, 24]. Mizumoto et al. have summarised their experience from the 1980s up to 2016 in a review beautifully documenting the advances in technology and philosophy that have developed their institutional protocols so far [25]. Their reports

over time have consistently documented a 3-year local control rate of 85%–90% and a 3-year OS from 50% to 60%. Passively scattered protons were used along with implanted fiducials, respiratory synchronised fluoroscopy and an in-house respiratory-triggered gating technique, which was used to manage respiratory excursion of the tumours efficiently. In 55 patients with HCC in the central portal region, Mizumoto et al. found 3-year local control and overall survival rates of 86% and 50.0%, respectively, without severe late toxicities (including bile duct stenosis) [26]. In a study of proton and carbon ion therapy for HCC from the Hyogo Ion Beam Centre, Komatsu et al. showed that both treatments achieved 5-year local control rates of 90%, with no significant difference between the two methods [27]. A systematic review of outcomes from PBT and other charged particle therapies (carbon ion) reported an LC rate of 86% at longest duration of follow-up as well as an OS of 79%, 59% and 37% at 1, 3 and 5 years, respectively [28]. They also compared outcomes with reported series of SBRT and noticed significantly more late toxicities among the SBRT group than the group receiving proton/carbon ion therapy (6.4% vs 2.5%; $p = 0.011$), while comparable efficacy was noted between the two. Specific subgroups where proton beam therapy was found to be helpful were in patients with poor liver function (Child-Pugh B), in those with large solitary tumours and in those with portal vein thrombosis [24, 29, 30].

Kim et al. have also reported their experience of risk-adapted PBT for HCC from the National Cancer Centre, Korea, with encouraging 5-year OS of 65.1%, 40% and 32.2% for BCLC Stage A, B and C, respectively [31]. The dose fractionation used in this study was also based on the proximity of the tumour to the gastrointestinal structures.

The group from the Harvard Medical School also systematically investigated the utility of protons in treating HCC and intrahepatic cholangiocarcinoma (ICC) with a feasibility study [32], followed by a Phase 2 trial [33]. This multi-institutional study reported by Hong et al. showed a 2-year local control rate of 94.8% in the HCC cohort with only two patients experiencing local failure and median OS of 49.9 months. This study delivered hypofractionated passively scattered proton therapy to patients with HCC ($n = 44$) to a dose of 67.5Gy in 15# (for peripheral tumours) or 58.05 Gy in 15# (for more central tumours). Almost 27% of patients had multifocal tumours and 30% had vascular invasion, and in spite of this, 2-year overall survival was very encouraging at 63%. The most common acute side effects were fatigue, skin rash, nausea and anorexia, and only four patients experienced grade 3 radiation-related toxicity. No grade 4/5 toxicities were seen.

A separate Phase III trial compared protons with TACE at the Loma Linda Hospital in California and has reported their interim analysis [34]. This showed a trend towards improved 2-year local tumour control (88% vs. 45%, $P = 0.06$) and progression-free survival (48% vs 31%, $P = 0.06$) favouring the proton beam treatment group. The most recent randomised Phase 3 trial with non-inferiority design from Kim et al. provides level I evidence of the ablative efficacy of PBT in small HCCs, by showing that PBT was non-inferior to RFA in this scenario [35].

Future Directions: In summary, proton beam therapy can safely reduce dose to the cirrhotic liver while enabling very high doses to be delivered to the HCC. It is

more efficient at this than the photon-based techniques especially in large tumours, patients with poor liver function and in those with portal vein thrombosis as well as in situations of re-irradiation. This is borne out of the excellent outcomes demonstrated in small institutional series and over long follow-up. A randomised controlled trial NRG GI003 is currently randomising patients with unresectable HCC to protons or photon-based irradiation, and its results are eagerly awaited.

9.5 Role of PBT in Cholangiocarcinoma

Unresectable cholangiocarcinomas form 50%–60% of patients at presentation. Doublet chemotherapy is the backbone of treatment of such tumours based on the results of ABC-02 trial, which resulted in a 3-month improvement of median OS (8.1 vs 11 months) [36]. However, this trial included a majority of patients with metastatic disease (74.6%), although the gemcitabine-cisplatin doublet improved survival even in the non-metastatic subgroup (HR = 0.47; 95% CI: 0.29–0.74). Meanwhile, several institutional series have demonstrated similar survivals with a combination of chemotherapy and radiation in various schedules [37]. However, the lack of level I evidence limits the applicability of this approach in the clinics. Specifically, approaches using stereotactic body radiation to escalate dose in unresectable cholangiocarcinomas have been reported to provide 1-year local control rates of around 78% and median overall survival ranging from 10.6 months to 35.5 months with a median value of 13.6 months and the pooled 1-year OS of 53.8% [38]. In this and other reports, it has been shown that dose escalation helps to improve outcomes [39]. However, significant gastrointestinal and biliary toxicity has been reported in attempts to deliver SBRT style doses to such tumours, especially hilar and extrahepatic cholangiocarcinomas but also intrahepatic cholangiocarcinoma. There has been interest in the use of proton beam therapy to deliver the same dose escalation to the intrahepatic tumour simultaneously with reduced doses to the normal liver and the adjacent bowel. Proton therapy has been explored more in intrahepatic cholangiocarcinomas than in hilar and extrahepatic because the homogenous density of the liver parenchyma results in homogenous dose distributions with passively scattered beam and there is not much dose perturbation due to heterogenous tissue densities in the beam path. Proton beam therapy is a technique that can deliver higher doses to these tumours while keeping dose to the liver, duodenum and stomach mucosa low. The previously mentioned Phase II trial from Hong et al. included more than a third of patients with intrahepatic cholangiocarcinoma and reported a local control rate of 94.1% at 2 years and overall survival of 46.5% at 2 years for ICC. Of the 39 patients with ICC or mixed HCC/ICC, six patients progressed during the period of follow-up, all having received <60 GyE. Most of these tumours were solitary (87.2%) with a median size of 6 cm, and two-thirds had received chemotherapy prior to PBT. Recently, Smart et al. have also retrospectively compared cohorts of patients treated with photons or protons during the same period [40]. PBT was found to have significantly improved

the overall survival as compared to photons (HR = 0.50; 95% CI: 0.25–0.98; $p = 0.05$). Long-term outcomes reported later confirm a 2-year local control of 96% and median OS at 21 months and a rate of 14% of grade 3 late radiation-related toxicity [41]. Ohkawa et al. from the University of Tsukuba also reported on the outcomes of 20 patients with intrahepatic cholangiocarcinoma (4 were metastatic and only 12 were treated with curative intent) who underwent passive scattered PBT to a median dose of 72.6 GyE in 22 fractions [42]. A substantial minority of patients survived >2 years, and the median survival in the curative group was 27.5 months. In terms of side effects, two patients had late grade 3 bile duct infections, and one had grade 3 bone marrow suppression, with no grade 4/5 events. Patients without jaundice had better outcomes. They recently updated their experience with a larger cohort ($n = 37$), which continued to show a median OS of 25 months in the curatively treated subset [43]. Makita et al. also reported a series of 28 patients treated with proton beam therapy with 1-yr OS rate of 49% and local control rate of 68% [44]. A biologically effective dose (BED) of >70 Gy was found to have better local control than lower doses, and grade 3 duodenal toxicity was found in 25% of the cohort within a year. However, their cohort included a higher proportion of perihilar and distal cholangiocarcinomas, which might account for the excessive luminal organ toxicity due to the proximity of the duodenum to these tumours. Hung et al. recently reported from Taiwan their experience with 30 patients, a majority of whom received concurrent chemotherapy too. The median dose was 72.6 cGyE, and the median OS was reported to be 19.3 months, with five grades 3–4 toxicities. In summary, proton beam therapy shows great promise in the management of unresectable, non-metastatic cholangiocarcinomas and, when combined with chemotherapy at least in some series, seem to be a safe and effective treatment modality.

Future Directions: Although great interest is already focused on protons as a means to dose escalate to intrahepatic cholangiocarcinomas, the additional dose conformality afforded by pencil-beam scanning with newer innovations in motion management is expected to increase the purview/applicability of proton beam therapy to extrahepatic cholangiocarcinomas also.

9.6 Role of PBT in Pancreatic Cancer

The role of radiation in improving local control in resectable, borderline resectable [45] and unresectable pancreatic cancers is now well defined, although its impact on overall survival is presently controversial. It is presently considered favourably in the adjuvant therapy of margin-positive (R1) cases [46]. In resectable and borderline resectable cases, while neoadjuvant chemotherapy improves overall survival [47], neoadjuvant chemoradiation seem to improve local control rates and enable more R0 resections [48], however at the cost of significant toxicity (52% serious adverse effects in the chemoradiation arm of the PREOPANC trial). The recent

American Society of Radiation Oncology (ASTRO) guidelines also strongly recommends definitive RT to be delivered for patients with unresectable or locally advanced pancreatic cancer without systemic progression following 4–6 months of chemotherapy [6, 49].

However, the effectiveness of conventional radiation therapy with photons in this site has hitherto been limited by the side effects such as nausea, vomiting, mucositis, duodenal ulceration/perforation, duodenal stenosis/stricture, liver and renal function compromise as well as hematologic toxicity caused by unwanted dose delivered to surrounding normal structures like the small bowel, duodenum, stomach, liver, kidneys and bone marrow. Due to their anatomical proximity to the pancreas, even sophisticated techniques of photon irradiation like IMRT and VMAT cannot reduce the dose to the duodenum so as to avoid toxicity completely. In this situation, proton therapy, which by its inherent dose deposition characteristics, has minimal dose beyond the end of range is an ideal modality to reduce side effects and improve tolerance of the treatment. This might even open up the window of opportunity to escalate dose to the tumour, thereby hopefully improving local control.

There are several dosimetric studies suggesting potential for reduction in dose to organs at risk with proton therapy compared to photon therapy in pancreatic cancer. When comparative plans were created for post-operative pancreatic cancer radiotherapy at the University of Pennsylvania, with 3D conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), volumetric-modulated radiation therapy (VMAT) and passive scattered and modulated scanned proton beams, it was seen that all the proton plans offer statistically significant lower doses to the left kidney (mean and V18Gy), stomach (mean and V20Gy) and cord (maximum dose) compared with all the photon plans. Additionally, modulated scanned proton therapy also provides lower doses to the right kidney (mean and V18Gy), liver (mean dose), total bowel (V20Gy and mean dose) and small bowel (V15Gy absolute volume ratio) than all the photon plans and passively scattered proton therapy [50]. However, in a similar study for patients with unresectable disease, Thompson et al. demonstrated reduced low to intermediate doses of radiation (<30 Gy) to organs at risk with passively scattered plans compared to VMAT plans, but not high doses (>30 Gy) [51]. Similar studies done at the Massachusetts General Hospital (MGH), Boston, also demonstrated that even in hypofractionated proton treatments, improved dose conformality resulted in significant sparing of the kidneys, liver and small bowel, evidenced by significant reductions in the mean doses to these structures [52].

Clinical data from MGH described a Phase 1 study in patients with resectable pancreatic cancer with the total dose safely escalated to 25 Gy in 5# using passively scattered protons [53]. No dose-limiting GI toxicity was noted in this study. Four patients experienced grade 3 toxicity including biliary obstruction, elevated bilirubin, shoulder pain and infection. A subsequent Phase 2 study also reported similar outcomes with 87% of patients able to undergo R0 resection and a 4.1% grade 3 toxicity rate [54]. Published literature from the University of Florida demonstrates that after proton therapy for resected (adjuvant), borderline resectable and

unresectable pancreatic cancer, at median follow-up of 11 months, there were no cases of grade ≥3 GI toxicity ($n = 22$) [55]. The same group also described a group of unresectable pancreatic cancer patients ($n = 11$), who received concurrent chemotherapy along with proton beam therapy and median survival reported was 18.4 months, of whom four patients were able to undergo resection after proton therapy, resulting in a median survival of 24 months [56]. The freedom from local progression at 2 years was 69%. The only post-operative complications were wound infection, ischemic gastritis and delayed gastric emptying seen in one (2%) patient each. These are significantly less than the rates of acute nonhematological toxicity reported from IMRT and in themselves warrant the use of this technology for better patient comfort during treatment.

The University of Pennsylvania reported their experience with 38 patients who received adjuvant radiation to the pancreatic bed compared with 67 patients treated during the same period with photons. Despite receiving higher doses, the proton group reported lesser grade 3 GI toxicity, although survival was similar [57]. The Mayo Clinic experience with unresectable pancreatic cancer also demonstrated that such treatments are feasible and safe even with pencil-beam scanned PBT. Thirteen patients with unresectable pancreatic cancer were treated with 50 Gy with pencil-beam scanning technique. When compared to VMAT plans, which were generated for backup, proton plans delivered significantly less dose to the duodenum, small bowel, stomach, large bowel, liver and kidneys. All the patients tolerated treatment well with no treatment breaks and no grade ≥3 adverse events. As median follow-up was 16 months, the estimated 1 year survival was 62% and the LC rate was 66% and four patients experienced local recurrence (all with simultaneous distant metastases as well).

The recent experience of the University of Tsukuba, Japan, strongly corroborates the expected improvement in clinical outcomes with dose escalation as the group reported 2-year overall survival rate of 50.8% (median 25.6 months) and 2-year local control rate of 78.9% (median > 36 months) with delivery of 50–67.4 GyE in 25–33 fractions in 42 unresectable locally advanced pancreatic cancer patients treated with proton beam therapy. All acute toxicities ≥grade 3 were hematologic, while severe acute and late gastrointestinal tract adverse events were not observed. Higher dose delivery to the tumour with proton beams safely lead to longer LC and OS [58].

Kim DY et al. have retrospectively reported the outcome of 37 patients with unresectable pancreatic cancer, treated with hypofractionated proton therapy with simultaneous integrated boost [59]. High- and low-risk volumes were treated to a dose of 45 GyE and 30 Gy, respectively, in 10 sessions, over 2 weeks. Patients variably received induction, concurrent and/or adjuvant chemotherapy. The median survival was 19.3 months and was significantly higher in patients receiving induction chemotherapy. The actuarial 1-year loco regional control and overall survival rates were 64.8% and 75.7%, respectively. Remarkably, no early or late grade 3 toxicity was noted.

In summary, in pancreatic cancer, proton therapy reduces side effects of therapy in the adjuvant or definitive setting of treatment of resectable, borderline or unresectable stages of the disease. It may also be able to safely improve local control outcomes by enabling dose escalation.

Future Directions: Dose escalation is being investigated at the University of Florida [60] and at the University of Maryland [61] for locally advanced pancreatic cancer that is unresectable or borderline resectable, with concurrent chemotherapy.

9.7 Role of PBT in Colorectal Tumours

The colon itself is a very sensitive structure, and radiation plays a very peripheral role in the primary management of colon cancer. Several dosimetric studies have shown benefit in irradiation of primary rectal cancers in the preoperative setting with some studies showing improved sparing of the bladder, small bowel and bone marrow [62], while others showed sparing of the small bowel and bladder only [63–65]. This may be beneficial in a subset of patients who are either receiving total neoadjuvant therapy and have already been pre-treated heavily with chemotherapy or who are keen to attempt non-operative management and in whom there might be a rationale for escalating dose to the primary [66], although it is not clear that dose escalation with external beam radiation alone improves clinical complete response (cCR) rates.

A small series of preoperative proton therapy for patients with rectal cancer has been reported in abstract form by the University of Trento and the University of Pennsylvania, reporting minimal side effects [67].

The role of protons in recurrent rectal cancer has been investigated further due to the potential for better sparing of normal tissues in the situation of re-irradiation. Local pelvic recurrences are highly morbid, and re-irradiation with photons in this situation is associated with high toxicity rates [68]. The University of Pennsylvania experience in seven patients treated with proton re-irradiation was reported by Berman et al. in 2014. Six patients received concurrent chemotherapy too, and after receiving a median cumulative dose of 109.8 Gy RBE from both courses of radiation, three patients experience acute grade 3 or higher toxicities, and three experienced late grade 4 toxicity. Doses received by bowel were significantly reduced.

Another report from Osaka reported two cases of locally recurrent rectal cancers treated with protons; one recurred locally in 2 years and died eventually, while the other remained free of disease after irradiation for >2.5 years [69]. Ogi et al. reported in 2018 outcomes of re-irradiation with protons for locally recurrent cancers [70, 71].

Future Directions: In locally recurrent rectal cancers, the PANDORA trial [72] is currently investigating the benefit offered by particle therapy in a systematic manner. Investigation into the use of protons as a component of total neoadjuvant therapy (TNT) may also be worthwhile.

9.8 Role of PBT in Liver Metastases

Historically local therapy to metastatic disease in the liver was considered counter-intuitive, but the emergence of more effective systemic therapy has brought local therapies into focus once again. The 5-year survival with resection for colorectal liver metastases is reported to be 40%–60% [73, 74], and photon-based SBRT has also reported 2-year survivals ranging from 30% to 73% [75]. While metastases from other primaries seem to be controlled with lower biological dose, a definite dose response has been demonstrated for colorectal liver metastases with better outcomes being seen with tumours receiving more than 100 Gy BED ($\alpha/\beta = 10$) [76]. In this context, proton therapy has the potential to escalate doses to the gross tumour while keeping the normal liver doses within safe limits. Specific subgroups in which it may be more beneficial than SBRT may be for large tumours, centrally located lesions or in situations of re-irradiation. Colorectal liver metastases very often do recur, and the use of proton therapy enables minimal low to intermediate doses to be deposited in the normal liver, thus allowing patients to be considered for retreatment due to minimal accumulated normal liver doses.

A dosimetric comparison of stereotactic photon-based versus proton-based planning for liver metastases revealed significant reduction in mean doses delivered to the normal liver in both small and large tumours, with a relative increase in the sparing of the liver as the tumour size increased [77]. It was also estimated that the risks of radiation-induced second malignancies was lower with proton-based SBRT rather than photon-based SBRT, based on the reduced integral dose deposited by protons [78].

Colbert et al. reported from MD Anderson and MSKCC on the possibility of using proton beams to deliver right hemi liver radiation therapy to five patients with bilobar colorectal liver metastases planned for two-stage hepatectomy [79]. These patients initially had chemotherapy followed by resection of the metastatic lesions in the future liver remnant (FLR) and portal vein embolisation of the opposite lobe but were deemed unsuitable for the second stage hepatectomy due to inadequate liver hypertrophy. The lesions in the remaining hemi liver were then irradiated with proton beams safely resulting in local control in all but one patient ($N = 5$), who received slightly lower doses.

Fukumitsu has published the largest retrospective series of patients with liver metastases from multiple primaries (colorectum, 43%) ($n = 140$) and reported 2-year and 5-year survivals of 46% and 24%, respectively, with median survival of 1.6 years [80]. About 133 patients, 35% of whom had solitary tumours only in the liver, with 4 cm median size of tumours, were treated to a median dose of 70 Gy RBE using a respiratory-gated passive-scattered proton beam. This resulted in a 5-year local control rate of 53% in 124 evaluable patients and a 5-year survival of 30% in 63 patients treated with curative intent (rather than palliative intent). Seven patients could not complete treatment, and 10 patients developed late toxicity (rib fracture, 1; cholangitis,1; decline in Child-Pugh score >2, 8).

Several retrospective reports of PBT in metastases from gastric cancer [81, 82], oesophageal cancer [83, 84] and breast cancer [85] mention survival rates at 3 years of 73%–78% and local control at 3 years of 71%–86%.

Hong et al. published results of the largest prospective Phase 1/2 clinical trial on stereotactic proton therapy for liver metastases in 2017, where the investigators described the importance of tumour genotype also. Out of 89 patients, 34 were colorectal liver metastases, and a maximum dose of 50 Gy in five fractions was delivered (BED_{10} = 100 Gy). The median tumour size was 2.5 cm, and majority (61%) had solitary tumours; however, 24 tumours (16.8%) were 6 cm or larger in size [86]. With no grades 3–5 radiation-related toxicity, 3-year local control and overall survival rates were 61.2% (95% CI: 50.8–71.5%) and 20.8% (95% CI:12.4%–30.8%), respectively. Colorectal metastases had worse LC than other tumours, and KRAS mutant and/or p53 mutant tumours did significantly worse than KRAS and p53 wild-type tumours, due to inherent radio resistance. Large tumours (>6 cm) fared similar to smaller ones, presumed to be due to the ability of proton-based SBRT to ensure liver dose constraints are maintained even in large tumours, which would be difficult in photon-based SBRT. Of note, the local control in this series was relatively low compared to other SBRT series and was attributed to doses ≤100 Gy BED_{10}. Hence, dose escalation using protons especially in colorectal metastases is an area worth further investigation.

Kang et al. of the Loma Linda University Medical Centre conducted a Phase I trial to determine dose-limiting toxicity for patients with 1–3 liver metastases treated with proton therapy [87]. While dose-limiting toxicity was not reached for maximum planned dose in the study (60 Gy in three fractions), a significant proportion of the liver, ranging from 523 cc to 1361 cc received <0.1 Gy.

9.9 Role of PBT in Anal Canal Carcinoma

Carcinoma of the anal canal is treated with a combination of radiotherapy, mitomycin C and 5FU with excellent local control rates and overall survival. The regime is however associated with toxicity due to irradiation of the bowel, bone marrow and skin of the groin; the rate of grade ≥ 2 reactions was 73% in RTOG 0529, which investigated the benefit of IMRT in the treatment of anal canal carcinoma [88].

Dosimetric studies carried out with scanning proton therapy, an older proton therapy technique, have demonstrated significant reduction in the mean dose to the bone marrow, bladder and bowel, both in the ideal scenario as well as on accounting for uncertainty related to positioning and range of protons [89]. This advantage is maintained when assessing the volume of these structures receiving low-dose radiation, the latter being associated with the risk of bowel and bone marrow toxicity especially with concurrent chemotherapy [90, 91]. The largest benefit (>90% reduction) was however noted in the dose received by the genitalia, indicating that proton therapy would lead to reduction in sexual dysfunction following radiation.

Dosimetrically, proton therapy plans were noted to be superior to VMAT and IMRT plans by Kronborg et al. [92] and Meir et al. [93] especially with regard to sparing of the pelvic bone marrow.

Clinical outcomes have been reported in a feasibility study of the more sophisticated pencil-beam scanning proton therapy technique by Wo et al. who noted a

halving of grade 3 dermatologic toxicity compared to a previously reported IMRT-based RTOG study. The authors noted a colostomy-free survival and overall survival rates of 72% and 80% at 2 years [94].

In an interesting case series, Buchberger et al. reported using pencil-beam scanned proton therapy for sparing the pelvic kidney in four patients who developed anal canal cancer following renal transplant. The mean kidney dose of the transplanted pelvic kidney was <1 Gy in three of four patients [95].

Future Directions: Proton beam therapy has been demonstrated to be feasible and safe in anal canal cancers with expectation of decreased normal tissue side effects. These findings hope to be validated in larger studies/registries. A prospective Phase II study at MD Anderson Cancer Centre is currently investigating the clinical value of advanced techniques of IMPT in newly diagnosed anal canal cancers to this end [96].

9.10 Conclusions

In conclusion, proton beam therapy has been studied in most gastrointestinal cancer subsites and indications for radiation and shows dosimetric and/or clinical benefit in most of them. With the emergence of pencil-beam scanning techniques, the implementation of proton therapy would become easier, and the technology would be expected to become more easily available throughout the world. So it may be expected that costs related to this technology will become lower, as this is one of the factors that restricts its wide use at present. With the use of proton therapy, radiation in GI cancers will be expected to become less toxic and hence more widely accepted and applied. The initial clinical studies in most sites do already reflect this outcome. Further studies will be needed with respect to dose escalation to tumours while maintaining minimal toxicity to the normal tissues. These will hopefully combine to improve the outcomes for these aggressive cancers while maintaining a good quality of life.

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Editorial Comments

Multimodal therapy has long been shown to improve survival in common gastrointestinal malignancies such as gastro-oesophageal, pancreatic and hepatocellular carcinomas. Both chemotherapy and radiotherapy are used in this. Radiotherapy has been used with or without concomitant chemotherapy (usually for its radiosensitising effect). The problem of radiotherapy in the management of gastrointestinal cancer is high toxicity related to undesirable

radiation to surrounding non-tumour-bearing organs such as the lung and heart in case of oesophageal cancers; small bowel, liver, kidneys and heart in gastric cancer; and normal liver surrounding the tumour-bearing area of the liver, stomach, small bowel and kidneys following radiotherapy for hepatocellular carcinomas and stomach (causing ulcer with not too infrequent incidence of severe gastrointestinal bleeding), bile duct (stricture, cholangitis) and duodenum (radiation induced stenosis). All these effects are noted with the use of conventional radiotherapy.

With the advent of proton beam radiotherapy, this has changed. This is related to the nature of proton particles—these concentrate on the target volume on its entering path and diminishing maximally at its exit. The result is obvious tumouricidal to the target sparing maximally the surrounding critical organ(s). Thus, proton beam therapy has given us hope in managing gastrointestinal cancers more efficiently. Researchers are continuously striving to improve, and we are sure we will see even better results in the not too distant future.

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Chapter 10
Immunosuppression in Liver Transplantation

Philip G. Thomas and Ravi Mohanka

10.1 Introduction

Successful application of transplant surgery for definitive management of end-stage organ disease occured while our understanding of immunology was still rudimentary. Immunosuppression was developed by surgeons, about the middle of the last century, battling with biological forces that nobody understood and often in the face of opposition from those who thought they did. The primary function of the immune system—to defend the body from invasion by foreign organisms—was being 'suppressed', and that could only have deleterious effects! The undeniable success of transplantation however led to a considerable evolution of our knowledge of how the immune system works, especially of our understanding of mechanisms that terminate an immune attack and regulate balance within the immune system. Today, the term 'immunomodulation' might be better than the older 'immunosuppression' to describe what makes a transplant work.

Making a transplant work has primarily been the responsibility of surgeons. Nowhere is this more true than in liver transplantation. The surgical skill required is a high-order combination of different surgical disciplines, including GI surgery, vascular surgery, and microvascular surgical techniques. Intraoperative anaesthesia, management of coagulopathy, and postoperative intensive care of these patients require skill, a dedicated team, and the accumulation of experience. Immunosuppression in this cohort of patients, who present difficult management problems related to fluid volume, ventilation, nutrition, and infection, adds a level

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of complexity that is perhaps greater than any other commonly encountered situation in modern medical practice.

This article will address only one aspect of the above. However, the pivotal role of immunosuppression in the success of liver transplant was recognized when the early dismal survival rate of 30%, doubled with the introduction of cyclosporine-based immunosuppression, and led to the 1983 consensus that liver transplant was no longer 'experimental' and deserving of broad clinical application [1, 2]. Like surgery, immunosuppression is a skill requiring regular, diligent practice. The attempt here will be to outline key principles of immunology, important to understanding the biology of transplantation, to discuss the basics of immunosuppression, and to perhaps build a platform for future innovation. Also, since the practice of immunosuppression varies between different regions of the world and is influenced by ethnicity, environment, prevalent diseases, and whether the donor is living or deceased, this article will also document the current state of the art as practiced by experts in India in the field of liver transplantation.

Achieving a balance between rejection on one side and infection on the other is central to the art of immunosuppression. It is built on the foundation of regularly updated basic sciences and learned through years of clinical practice with a master.

10.2 Discovering the Immunobiology of Transplantation: A History

An organized approach to understanding the science of transplantation starts in the twentieth century when the term 'graft failure' finds first mention [3]. Prior to this, transplantation was the stuff of miracles and legends.

Early attempts to take organ transplantation from animal to human experiments involved a vascularized organ, when human kidney transplant was attempted in 1933 Soviet Russia. The rapidity with which these grafts were lost pointed to some 'innate' mechanism, an *innate immune response* the recipient was born with. In hindsight, these grafts probably met with preformed ABO antibodies, and failure is attributed to the lack of understanding, at the time, of major blood groups [3].

We know, however, that Karl Landsteiner had started working on blood transfusion in the 1890s in Vienna and, by 1909, had described the major blood groups. Nevertheless, it was not until 1930, after he had moved to the Rockefeller Institute in New York and won the Nobel Prize, that blood transfusion medicine developed. Recognizing blood types, and 'humoral' mechanisms, not visible to the naked eye, that could cause destruction of mismatched blood cells was key to successful blood transfusion, hitherto considered taboo. World War 2 saw the establishment of blood banks, and transfusion became a common practice.

Attempts to transplant skin followed the above and were driven by wartime necessity of resurfacing wounds and burns in World War 2. Unlike mismatched blood, first time skin grafts were not immediately destroyed, suggesting that

adaptive and not innate mechanisms were at work when tissue was involved. Skin is nourished by lymph preceding neovascularization, and lymph contains lymphocytes! Rejection of the skin allograft was associated with invasion of the donor's skin graft by host lymphocytes, over the next 4 or 5 days. This process, visible under the microscope, led to the recognition of lymphocytes and cellular mediators of the *adaptive immune response*.

Peter Medawar, a 'Brazilian-born British citizen of Arab extraction', is generally credited with recognizing the importance of the lymphocyte while working on transplanting skin from human donors to save the lives of burned aviators in Oxford, UK. His precision in experimentation, writing, and speaking made him the central figure in the emerging field of transplantation, although Loeb, an émigré from Nazi Germany and Chief of Pathology at Washington University, St Louis, may have actually preceded him in recognizing a role for lymphocytes [3].

The term 'rejection' was now used to describe graft failure caused by immunological processes.

Cellular and humoral processes in allograft rejection were recognized by the end of World War 2. Genetic diversity posed a significant problem, but there was hope from the experience with life-saving blood transfusions, where genetic dissimilarity could be managed by recognizing antigens and antibodies and by observing the rules of ABO blood type compatibility and matching.

Recognizing and naming 'tissue antigens', the antigens on nucleated cells, and understanding the value of tissue type matching in bone marrow and solid organ transplantation were still a few decades in the future.

10.2.1 Controlling the Immune Response

Immediate destruction of ABO mismatched blood, indicating an innate barrier the individual was born with, was by now well recognized. With respect to solid organs, the species barrier causing rapid destruction of xenografts was also recognized during animal experiments. While the existence of barriers to transplantation were recognized, the actual process—the nature of the antigens involved, the process of antigen recgnition, and the mechanism of cell destruction were yet to be discovered.

Within the same species, genetic diversity, however problematic, did not always result in immediate graft loss. Cortisone, developed by Billingham, a Medawar's graduate student, could attenuate the adaptive immune response to allografts in animal models. Following the experience of destruction of immune cells by widespread nuclear radiation, at the end of World War 2, radiation was seen as a means of controlling the adaptive immune response, or preventing it from happening in the first place. Total body irradiation (TBI) prior to engraftment was proved to work in animal models [3].

In humans, however, genetic diversity between donor and recipient was considered such a great barrier that completely bypassing the rejection response by transplantation between identical twins was the only way forward. Successful kidney

transplantation between twins was carried out by Murray on December 23rd, 1954. No anti-rejection treatment was required. This work, although it attracted a great deal of attention worldwide, had no real scientific significance [3]. What had now been proved in humans was a concept well established in animal models, and the surgical technique used was also well established in prior attempts in humans [3].

Meanwhile, the clinical need for transplantation had grown. Dialysis for renal failure developed about the same time that blood banking became an established practice, and there was suddenly an increasing cohort of patients on chronic dialysis needing kidney transplant.

To be able to successfully transplant organs between genetically dissimilar individuals was the only practical solution to the above need, and more surgeons were drawn to attempt kidney transplantation. Attempts were made to extend Murray's success to fraternal twins, or to transplants between family members. However, in the subsequent decade, these attempts were met with poor outcomes and a rising tide of opposition to what was seen as human experimentation.

What kept the dream alive was the observation that 'chimerism', the stuff of legends, did actually exist in nature. Cell lines of more than one distinct genotype derived from different zygotes were identified to coexist in a single individual [4], holding out the promise that an organ transplanted from a genetically different individual could coexist within the recipient's body [5].

10.2.2 Tolerance

Tolerance, or immunological non-reactivity was described by Medawar and Billingham to alloantigens, and the concept was extended to self-antigens by the Australian Macfarlane Burnet. There were mechanisms by which the immune response could switch off to some antigens while remaining normally active towards others. This concept revolutionized the field of immunology. For this work describing 'actively acquired tolerance', they jointly received the Nobel Prize in 1960 [5].

In his Nobel lecture December 12, 1960, Medawar described 'rejection' as the immunological response that prohibits grafting of tissues between individuals of different genetic make-up. More importantly, he went on to define 'tolerance' as a non-reactivity caused by exposing animals to antigenic stimuli before they were old enough to undertake an immunological response, i.e. while the immune system was naïve.

He had made this discovery in cattle.

Twin pregnancies in cattle are rare, and the twins are usually fraternal, not identical. When the fraternal twins are of opposite sex, the female is referred to as a 'freemartin', recognized as a problem for cattle owners/breeders because she is infertile. The English surgeon John Hunter in 1779 had performed anatomical dissections on freemartins and found they had masculinized or rudimentary sex organs. Explanation for this phenomenon had to wait till the early twentieth century when dissection of a pair of unborn cattle twins revealed the placentas were fused and

they shared a common intrauterine circulation, allowing blood to be freely exchanged between the developing twins. Medawar and Billingham, working with freemartin cattle, described successful transplant of skin grafts between the non-identical fraternal twins without rejection. Non-reactivity to cells and tissues of the donor occurred and was maintained while retaining the ability to reject tissues from another donor. Cells of donor origin were found circulating in the recipient, indicating donor-recipient chimerism had occurred and was considered a necessary condition for tolerance to occur. Subsequent experiments with other species showed that chimerism could be induced by exposing the fetus' naïve immune system to cells of a genetically non-identical member of the same species.

It was this work of chimerism induction to prevent graft rejection that led to the Nobel Prize being awarded to Medawar, and it reverberates to this day in immunosuppression trials to induce tolerance [3].

Macfarlane Burnet, a microbiologist who had noted that mice with congenitally acquired lymphocytic choriomeningitis virus would not mount an immune response against it, postulated imaginatively that 'If, in embryonic life, expendable cells from a genetically different race are implanted and established, no antibody response should develop against the foreign antigen when the animal takes on an independent existence'. [5].

10.2.3 Early Clinical Immunosuppression

In the decade that followed the success of Joseph Murray, several attempts were made around the world to extend kidney transplantation to genetically non-identical individuals. Methods used to weaken the immune response in animal models were attempted in human patients and included total body radiation (TBI) and bone marrow inoculation to induce chimerism. The results were extremely discouraging, with <10% of several hundred allograft recipients surviving as long as 3 months [3].

Clearly, TBI in a patient with end-stage renal failure was not a good idea. The chimerism induced by concomitant bone marrow inoculation was unable to prevent graft loss. Using drugs to deplete lymphocytes appeared intuitively to be a better option, and azathioprine, a derivative of 6-mercaptopurine developed by Hitchings and Elion in 1954, was introduced by the pioneer Murray along with Roy Calne, his research fellow from England. Calne's signal contribution was to demonstrate the effectiveness of azathioprine in prolonging the survival of canine renal transplants.

Nobody really knew, however, how to manage clinical immunosuppression. At an international conference in 1963, organized by the National Research Council, to review the data of the first decade of clinical transplantation, the mood was gloomy, with several participants questioning whether it was justified to continue transplantation [3].

Only one presentation stood out: Tom Starzl, 'a virtually unknown newcomer' to the field, presented his data from Denver, showing over 70% renal graft survival at

1 year. He had a new method: charts detailing the daily progress of each individual, including laboratory tests, urine output, and immunosuppressive drug doses.

Starzl's famous 'wall charts' are perhaps the first example of the successful use of checklists in medicine. Decades later, the value of checklists and wall charts 'to make the reliable management of complexity routine' is widely recognized [6].

He was using a combination of azathioprine and steroids, as maintenance therapy, and large doses of prednisone to reverse rejection. He showed that not only could rejection be reversed, many patients then went on to have normal renal graft function on minimal doses of immunosuppression. The outlook for clinical transplantation changed completely with Starzl's report. Within a year, 50 new transplant programs began in the United States alone, and all adopted Starzl's 'immunosuppression cocktail' [3].

Apart from using immunosuppressive drugs in combination, clinical immunosuppression would now be thought of in distinct phases: **induction** and **maintenance**, for which different strategies are required. Circulating lymphocyte depletion by thoracic duct cannulation-drainage (for up to 3 weeks!) prior to engraftment was shown to eliminate graft loss in living donor and cadaveric renal transplantation [7, 8]. Escalating protocols for management of rejection based on grading the histological findings were introduced.

Several patients in Starzl's original series came off all immunosuppression, with grafts surviving over 40 years. Starzl's fellows in Pittsburgh, including both authors of this paper, have seen and managed these patients, when admitted to hospital for 'microchimerism studies' to demonstrate donor origin lymphoid cells in their blood, bone marrow, and skin. Celebrations at the University of Pittsburgh auditorium would have these living examples of tolerance, the ultimate hope of clinical transplantation, and immunosuppression, in seats of honour as pioneers along with their surgeon.

10.3 Current Concepts in Transplant Immunology

A full-blown immune response requires the participation of both the innate and the adaptive immune systems.

Vaccine developers have known this all along. Injecting pure antigen does nothing. Adding a non-specific irritant, like alum, results in a sterile inflammation, attracting elements of the innate immune system, which then sets in motion the full-blown immune response with participation of the adaptive system, and creation of immunological memory.

Traditionally, greater importance was given to the adaptive immune system in the context of human organ transplantation. The T- and B-lymphocytes involved in adaptive responses have been well-studied, understood, and have had effective therapies directed against them to enable graft survival.

However, efforts to understand the problem of *chronic* graft loss even in the presence of adequate immunosuppression directed against adaptive immune

responses have led to increasing interest in the innate immune system and the early non-specific responses that trigger specific adaptive responses. Persistence of macrophages, involved in the initial inflammatory response to cell death and circulating cell-free DNA, are implicated increasingly in long term allograft injury and loss [9].

10.4 Innate Immune System in Transplantation

Innate immune responses are present from birth, not learned, adapted, or permanently heightened as a result of prior exposure to foreign antigen. It is thought that the innate system is designed to protect the host from the time of initial exposure to when the adaptive responses kick in over subsequent days or weeks. The objective is to reduce the load of foreign antigen by phagocytosis and direct killing [10].

The innate immune system can recognize 10^3 molecular antigenic patterns. Foremost, among these are oligosaccharide Gal antigen present on cell surface of different species (xenografts). The destructive power of the innate immune response is clearly seen in the hyperacute rejection with which xenografts are attacked by natural killer (NK) cells and macrophages acting directly or with complement fixing antibodies in the 'antibody-dependent cellular cytotoxicity' (ADCC) pathway and proteins in the coagulation cascade [11].

In the context of human organs (allografts), innate immune activation results from tissue injury. Ischaemia and reperfusion result in cell death. Injury to the vascular endothelium of the graft and the microcirculation occurs during transplantation and can increase the severity and duration of ischaemic injury. Cell-free DNA and purine (ATP) released by necrotic cells circulate freely in the donor, resulting in the priming and activation of the immune system in the recipient [12].

Donor organ parenchyma releases damage-associated molecular patterns (DAMPS) following cell death. These are powerful stimulants of the innate immune response and are sensed by recipient monocytes and macrophages [9]. DAMPS bind to cell surface receptors called pattern recognition receptors (PRRs) linked to cell signalling pathways that regulate inflammatory genes that control the generation and secretion of cytokines and other immune molecules in response to foreign antigen. The generation and secretion of chemotaxic substances, like selectins and integrins, promote migration of a large number and variety of leukocytes to the site of the inflammatory response [10].

Activation of the complement cascade, a tightly regulated network of proteins, may also occur [9]. Typically associated with blood type mismatch and the formation of antigen-antibody immune complexes, complement-mediated injury can manifest as disseminated vascular permeability and anaphylactoid reaction. As the cascade progresses, cleaving proteins in sequence, formation of the terminal membrane attack complex (MAC), C5b-9, results in drilling holes in cell membranes, leakage of intracellular contents, and cell destruction.

Clinical recognition of innate immune system activation used to be common with deceased donor organs before brain dead donor management improved and is still encountered today in the context of organ donation after cardiac death. It is also responsible for immediate graft failure in cases of accidental transplant between ABO incompatible individuals.

This component of the recipient immune response may be easily forgotten if live donor transplants constitute the bulk of clinical practice.

Controlling the innate immune response is the basis for using more aggressive immunosuppression protocols in recipients of deceased donor grafts, as compared to live donor grafts.

In the context of kidney transplantation, where delayed graft function (DGF) and primary non-function (PNF) are more clearly defined than in liver transplantation, deceased donor kidney recipients usually receive powerful lymphocyte ablative immunosuppression upfront. It is well recognized that the adaptive immune response in individuals, who do develop features of early graft injury mediated by the innate system, is also skewed towards greater B-cell responses with antibody production against donor antigens. These recipients are more prone to development of donor-specific antibodies over time, which are implicated in chronic graft loss.

Although antibody-mediated rejection (ABMR, or AMR) is uncommon in liver transplantation, this experience has translated into immunosuppression protocols that are higher for deceased donor liver transplantation (DDLT), than for live donor liver transplantation (LDLT).

The destruction caused by innate immunity is so severe, widespread, and difficult to control that at this time the only practical approach is to try and avoid it altogether.

Situations in which a heightened innate immune response can be anticipated include:

- A deceased donor in whom blood pressure control has required two or more pressors for over 12 h
- Donation after cardiac death when the ‘agonal time’ exceeds half an hour, or the warm ischaemia time between cardiac arrest and institution of core cooling takes more than 15 min.
- Hypernatremia in the donor at any time during the course of the admission prior to death, particularly if it could not be corrected prior to organ retrieval. Extreme hypernatremia is not uncommonly encountered when donors with catastrophic brain injury (widely defined as GCS <8 on admission, or <3 after initial resuscitation) are managed with intensive diuretic therapy, especially when development of diabetes insipidus (defined as urine output over 5 cc/kg in 1 h) goes unrecognized.
- Fatty liver (>50% fat) in the donor. Cooling the liver for preservation after retrieval can result in wax-like solidification of the intra-hepatic fat with destruction of the microcirculation. Such donor livers are usually not accepted for transplantation or, in more recent times, subjected to normothermic preservation on a pump to avoid the microcirculatory injury caused by cooling.

– Warm ischemic injury to a graft, common in donation after cardiac death; or, in the context of live donor liver transplant, due to some intraoperative event leading to a period of graft ischaemia following rewarming.

Strategies to limit innate system immune responses include:

– Expert ICU management of the 'potential organ donor' to limit hypotension and avoid cardiac arrest prior to organ retrieval.
– Limiting the duration of warm ischaemia, and cold ischaemia, during the process of organ retrieval in the donor and implantation in the recipient.
– Effective core cooling of the liver during organ retrieval in the deceased donor, by in situ perfusion of the preservation solution via portal vein and hepatic artery or by rapidly cooling the organ on the back table via the portal vein after removal in the live donor.
– Development of better organ preservation solutions with IL-10 gene delivery during organ preservation has been tried in the context of lung preservation, to reduce the inflammatory response following implantation [9].
– Pump perfusion can wash out the products of cell death and preserve the microcirculation better than preservation in ice slush [12]. In the context of kidney transplantation, this has not only reduced early graft dysfunction but also improved long-term graft survival [13].
– Constant vigilance to prevent accidental blood type incompatible transplantation.

10.5 Adaptive Immune System in Transplantation

The timeline of onset of the adaptive immune response is about 96 h after first exposure to foreign antigen. Also called acquired immunity or specific immunity, this system is only found in vertebrates. It is specific to the antigen presented, to which it has the capacity to develop memory [14].

Unlike the innate immune system, which recruits a diverse number of immune active cells, the adaptive system relies almost totally on lymphocytes. Lymphocytes are of two types: T- and B-cells. Both cell lines originate in hematopoietic stem cells within the bone marrow, but T-cells, after migration, mature in the thymus.

The term 'rejection' is used to describe the recipient's immune response to foreign elements that are present on the transplanted organ. These elements are proteins that differ between donor and recipient and are called alloantigens, and the response mounted against the organ is called the alloimmune response.

The principal alloantigens are human leucocyte antigens (HLA), which are of two classes: class I (HLA A, B, and C) is expressed on all nucleated cells, whereas class II molecules (HLA DP, DQ, and DR) are expressed only on immune active cells, e.g. APCs (dendritic cells, macrophages and other phagocytic cells, and some B-cells), activated T-cells, and endothelial cells [15].

T- and B-lymphocytes are responsible for rejection, with the T lymphocytes playing the principal role. Experimental animals devoid of T-cells do not reject allograft organs or tissues [16].

T-cells express a series of unique antigen-binding receptors on their membrane, known as the T-cell receptor (TCR). The genes that code for components of the TCR are arranged and rearranged with so much diversity in the course of development (ontogeny), that humans carry a large repertoire of T-cells that can recognize and react to virtually any foreign protein [16].

Each T-cell expresses a single type of TCR. The TCR does not 'recognize' or bind to whole antigens, but to small peptides derived from the foreign antigens. These then have to be presented, in the context of the HLA molecules on infected cells, on the surface of antigen presenting cells (APCs).

Dendritic cells usually, but also macrophages, B-cells, fibroblasts and epithelial cells function as APCs.

It is estimated that only 1 in 10,000 T-cells in a human being recognize peptides derived from any given microbe. On the other hand, the immune response to an allograft involves anywhere up to 10% of the T-cell repertoire, essentially 100 times more ammunition than that required for an antimicrobial response. In fact, T-cells capable of allorecognition are formed in abundance in foetal life where there is no danger of exposure to micro-organisms. It has been postulated that these may be vital components of mechanisms that help a foetus to defend against the maternal immune system, surviving for 40 weeks in the face of a potentially hostile maternal immune system without the need for immunosuppressive drugs [17]. This, however, also constitutes the dominant obstacle to improving allograft survival [16].

T-cells have the capacity to rapidly proliferate and differentiate if appropriate signals are received. Controlling signals are therefore key to preventing a runaway T-cell response.

In a primary exposure, T-cell activation has a high threshold, with stringent dependence on co-stimulatory molecules (see below), and this process can only be achieved within the secondary lymphoid organs—spleen or lymph nodes. On the contrary, a secondary immune response to an antigen previously encountered is mediated by memory T-cells and is significantly stronger and more rapid than the primary response and can occur not only in the lymphoid organs but also at non-lymphoid sites, e.g. within the allograft itself [14, 16].

The two main types of mature T-cells found in the circulation are T helper cells and cytolytic T-cells. T helper cells, also called Th lymphocytes, express CD4 molecules on the cell surface, while cytolytic T-cells express CD8.

B-cells, on the other hand, leave the marrow, expressing a unique antigen-binding receptor on their membrane. Unlike T-cells, B-cells can recognize antigens directly, without the need for APCs, through unique antibodies expressed on their cell surface [14]. The principal function of B-cells is the production of antibodies against foreign antigens. B-cells can also act as APCs (see above).

10.6 Allorecognition

During a transplant, cells of the donor's immune system within the organ are also transplanted, and the moment the organ is re-perfused within the recipient, these cells migrate into the recipient's circulation. The two immune systems thus 'see' each other for the first time, and T-cells of the recipient get to recognize the donor. This can happen in three different ways [15]:

- 'Direct pathway,' where APCs of donor origin, with donor alloantigens on their surface, are presented to recipient T-cells and T-cell recognition is activated. This pathway is estimated to be over 10 times as common as the 'indirect pathway' (see below) and is thought to be the major pathway responsible for acute rejection. Over time, APCs of donor origin are lost and replaced by APCs of recipient origin, and the risk of acute rejection is reduced.
- 'Indirect pathway' where recipient APCs acquire donor alloantigens and present them to recipient T-cells, leading to ongoing immune reactions. This is the pathway thought to be the pathway that leads to chronic rejection.
- 'Semi-direct pathway' where recipient APCs acquire intact donor APCs along with their surface peptides of donor origin and present them to recipient T-cells. The significance of this pathway in vivo has not been fully determined.

10.6.1 Site of Donor-Recipient Interaction

In the typical recipient, with no significant prior alloimmune experience, donor origin APCs migrate from the graft to recipient lymph nodes, where the recognition by naïve T-cells takes place along the direct pathway described above.

In the event that the recipient has already acquired immunity to the donor, either by prior transplantation or in the case of certain virus infections, where virus-specific T-cells can cross-react with certain alloantigens (e.g. HLA-B44), memory T-cell populations can interact with the donor organ within the organ itself and do not require antigen presentation in recipient lymphoid organs.

Implication for Immunosuppression:

Influencing APC function is one strategy of controlling the immune response. Currently, the most effective strategy to suppress non-specific inflammatory responses and reduce inflammatory cytokine expression by monocytes, macrophages, and dendritic cells, making them less efficient at presenting antigen and activating T-cells, involves the timely use of corticosteroids [15].

10.7 T-Cell Activation, Proliferation, and Differentiation (the Two-Signal Model)

Signal 1: T-cell activation occurs in the secondary lymphoid tissues, usually the draining lymph nodes, with the engagement of the TCR/C3 complex with the MHC:peptide complex presented by the APCs above-described.

Signal 2: Additional proteins, providing 'co-stimulation', are required to activate the T-cell, after the initial engagement. Two of these proteins, present on APCs, are:

- CD 40, a transmembrane protein present on the APC, which interacts with the CD 154 molecule present on T-cells (CD4+ T-cells, and CD8+ T-cells and NK cells).
- B7 proteins on the APC, which interact with CD28 molecule on T-cells.

Following the above, transcription factors in the cytoplasm (NF-AT) are activated that cause transcription, within the nucleus, of genes that code for cytokines. These molecules include IL-10, IFN-Y, IL-4, and IL-12 and, after production, travel out of the cell, circulate, and result in T-cell proliferation and signalling to recruit more T-cells. In addition, T-cell apoptosis is inhibited, providing protection from cell death induced by Fas pathway [18].

B-cells are also activated by CD40 and switch from producing IgM to IgG.

Acute cellular rejection, which usually develops a week after transplantation, is T-cell mediated with CD4 T-cells, playing a critical role in graft destruction. In addition, amplification of the response occurs via soluble cytotoxic factors like granzymes and perforins, leading to recruitment and proliferation of CD8 cells, capable of producing graft destruction.

10.7.1 Relevance to Therapy

The T-cell receptor or TCR has a cell surface marker called CD3, which is very specific to the TCR. Monoclonal antibodies to CD3 (e.g. muromonab or OKT3) are potent immunosuppressants inducing T-cell apoptosis by binding to the CD3 molecule. All subtypes, including naïve and memory T-cells, CD4 and CD8, are affected and eliminated, and circulating lymphocyte counts can be seen to drop precipitously.

Calcineurin inhibitors (CNIs), cyclosporin and tacrolimus, act on the cytoplasmic proteins present in T-cells, blocking calcineurin which is a calcium- and calmodulin-dependent phosphatase. This in turn blocks a family of transcription factors (NF-AT), leading to reduction in the transcription of the genes that determine the production of cytokines. As a result, the production of interleukins (IL2), CD40L, TNF alpha, interferon gamma, and granulocyte-macrophage colony-stimulating factor (GMCSF) is blocked. Ultimately, the proliferation of T-cells is reduced, without causing a reduction in T-cells required for protection against infections in the recipient.

While reduction in T-cells (by anti-T-cell antibodies like OKT3 or muromonab) may be required for the treatment of a full-blown rejection in process, a more gentle long-term control of T-cell proliferation, without elimination of T-cells is the better strategy for maintenance immunosuppression after successful engraftment. The calcineurin inhibitor group of drugs has revolutionized transplantation, by enabling

graft survival without profound immunosuppression causing susceptibility to opportunistic infections.

mTOR inhibitors are another class of drugs, of which sirolimus (Rapamune), first in the market, has been used widely in kidney transplantation. It has a warning (so-called black box warning, printed on the medication bottles) against use in liver transplantation. Everolimus, a more recent entrant of the same family, is increasingly used in liver transplantation. It is effective as a long-term maintenance medication but requires additional CNI administration to reduce risk of acute rejections in the early post-op period.

Mechanism of action: Following entry into the cytoplasm, sirolimus and everolimus bind to the FK-binding protein and presumably modulate the activity of mTOR ('mammalian target of rapamune') receptor. This inhibits interleukin (IL)-2-mediated signal transduction, resulting in cell-cycle arrest in the G1-S phase. While the CNIs—cyclosporine and tacrolimus—inhibit the production of cytokines that follow antigen recognition by T-cells, sirolimus and everolimus block the response of T- and B-cells to cytokines, preventing downstream activation and proliferation. This explains how CNI and mTORi drugs act synergistically to prevent rejection. Monitoring these drugs when used in combination is usually done by adding the drug levels of the two, to achieve or maintain the level considered optimal for either drug when used alone.

Everolimus and sirolimus also have antimalignancy potential, and this is useful in the long-term management of patients coming to liver transplantation with hepatocellular cancer on a background of liver cirrhosis.

10.8 B-Cell Activation and Proliferation

B-lymphocytes, responsible for initiating antibody production, are the basis of 'humoral immunity'. They arise from hematopoietic stem cells in the bone marrow or the foetal liver. The B-cell receptor (BCR), an immunoglobulin bound to the cell membrane, is such that each B-cell expresses a unique receptor, the so called 'one-cell/one-receptor/one-antigen' paradigm [19].

B-cells migrate to secondary lymphoid organs, where they mature, and wait for the chance to respond to their specific/designated antigen.

The immunoglobulin that constitutes the B-cell receptor is a protein formed by two pairs of heavy chains and 1 light chain, which are coded for by separate genes (termed VH, DH, JH, for the heavy chain, and VL and JL for the light chain) which can in theory produce more than 10^{11} different combinations corresponding to different antigen specificities. The antigen binding region on the immunoglobulin molecule is known as the variable or V region. The part of the molecule that engages the immune system is known as the constant region or C region.

Unlike T-cells which require the foreign antigen to be presented by an MHC, B-cells bind to the antigen directly.

Naïve B-cells which are inactive are stimulated by in coming antigen and go from the G 0 phase of the cell cycle to active or G1 phase. The proliferative burst that follows is called clonal expansion. B-cells then migrate to different areas of secondary lymphoid structures to communicate with other cell types, and effect the following functions:

– Initiate interactions with T-cells where they can take on the role of MHCs, and initiate T-cell mediated immune responses [20]
– Retreat into the germinal center when they may differentiate either into plasma cells producing copious amounts of antibody; or enter a quiescent phase as memory B-cells which have a very long life, capable of generating accelerated B-cell responses, which are the basis of antibody-mediated rejection in the context of transplantation.

Antibody-mediated rejection is B-cell mediated, and may occur as an **acute** process: Acute antibody-mediated rejection (ABMR), or as a *chronic* process, which results in chronic rejection.

The liver was once considered as a privileged organ that is not susceptible to antibody-mediated destruction, which is much more commonly encountered with Kidney, kidney—pancreas, and intestinal transplants. The liver is also able to prevent ABMR of intestinal transplants, which is much less common in a combined liver-small bowel transplant than when small bowel is transplanted alone.

ABMR is caused by preformed antibodies, ABO incompatibilities, or de-novo antibodies that develop after transplant [21]. Antibodies attack the vascular endothelium within the graft, and this has distinct features on histology: so-called vascular rejection. Donor-specific antibodies (DSA) can also be found in peripheral circulation.

The exact incidence of ABMR in liver transplantation is difficult to establish, mainly because of scepticism about whether it ever occurs, and hitherto there was no consensus or clear guidelines to the diagnosis. However, increasing evidence over the last 2 decades, along with the increasing application of ABO incompatible liver transplantation have increased the importance of diagnosing and treating ABMR, and the Banff working group on Liver allograft pathology, 2016 has assigned a scoring system to facilitate the diagnosis.

Chronic antibody-mediated rejection is even more difficult to diagnose because of a lack of specific clinical or histopathological features [21].

10.8.1 Relevance to Therapy

ABMR treatment in liver transplantation is a developing field, and lessons learned in kidney transplant are applied. These include:

– Removal of circulating antibodies by plasmapheresis.

– Administration of Intravenous immunoglobulins (IVIG) is done to neutralize circulating pathologic antibodies (anti idiotypic), as well as cytokines, anaphylatoxins, complement degradation products like C3a and C5a, and to block B-cell receptors [22].
– Immunosuppressive drugs:
  - High dose corticosteroids are most commonly used, along with IVIG and plasmapheresis.
  - Anti B-cell monoclonal antibodies, directed against B-cells (rituximab) have been found effective, and often combined with corticosteroids, IVIG and plasmapheresis.
  - Proteasome inhibitors (Bortezemib) used to treat myeloma, can induce apoptosis of plasma cells and reduce activated complement that is involved in antibody directed graft destruction. The latter has been found to be effective in reducing anti HLA antibodies in cases resistant to conventional ABMR measures.

10.9 Tolerogenesis

Alongside mechanisms that initiate and direct the destruction of an allograft, are those that regulate and control these immune responses. These occur at a slower pace, and cannot of themselves counter the destructive immune response [23]. It is, however, increasingly recognized that it is possible to approach immunosuppression in ways that will support natural autoregulation of the immune response, and promote tolerance, so-called 'Tolerogenic Immunosuppression'.

Immunological tolerance is the acquired ability for immune responses against a defined set of antigens to be abolished, even while the immune system continues to function normally in every way. It is basic to survival that immune cells not attack host tissue. It is recognized now that T-cell-mediated unresponsiveness is one of the key mechanisms responsible for tolerance [23].

The process of selecting T- and B-lymphocytes that will recognize foreign antigens and not attack antigens expressed on host organs and tissues begins in embryonic life. With T-cells, this occurs in the thymus (in a process called 'central' or 'thymic deletion') and also in the periphery (in a process called 'activation-induced cell death' or 'immune exhaustion'). It is possible to achieve central deletion of alloreactive T-cells by delivering the alloantigen into the thymus via direct injection. This method of producing 'central tolerance' and inducing a 'chimeric state' may presently be of experimental interest only but provides proof of concept that it is possible in an individual for two cell lines originating from genetically dissimilar zygotes to coexist.

Peripheral destruction of activated T-cells, activation-induced cell death (AICD), is of particular interest in transplantation for obvious reasons. The process is dependent on the TCR, wherein restimulation with the antigen engages Fas ligand (FasL

or CD95L), a transmembrane protein which then activates a family of protease enzymes called caspases, whose function is to produce programmed cell death or apoptosis.

Distinct from, but in addition to the deletional approach, is the generation of a population of T-cells called Tregs, that are responsible for immune regulation in vivo. Tregs are generated in the thymus, express CD25+ CD4+ foxp3 genes, and are an actively dividing and differentiated population that is maintained by self-renewal [23]. It is possible also to produce Tregs peripherally in response to alloantigen, and in individuals in whom Tregs are generated in abundance, they probably play an important part in maintenance of the graft over the long term.

Regulatory B-cells, or Bregs, first described in the 1980s, are a small subset of the total B-cell pool. They express high levels of CD1d, CD21, and CD24 and moderate levels of CD19. They have a characteristic ability to secrete IL10, and they suppress T helper cells from differentiating. There may be a link between Breg and T-cells, with Bregs acting as potent generators of Tregs [23].

10.9.1 Relevance to Therapy

The new millennium has seen the increasing use of powerful lymphocyte-depleting agents as 'induction therapy' with the objective of maximizing immunosuppression immediately prior to reperfusing the graft during transplantation [24]. The two most widely used drugs are:

- Thymoglobulin: Also called anti-thymocyte globulin (ATG), this polyclonal antibody is raised by injecting the New Zealand rabbit with human thymocytes.
- Alemtuzumab or Campath: This anti-CD52 monoclonal antibody is a chimeric (mouse-human), humanized monoclonal antibody that acts on all cells of the immune system that express CD52 surface antigen.

Thymoglobulin acts mostly on lymphocytes of T-cell lineage. It is administered in multiple divided doses (1.5 mg/kg) over the first few days post-transplantation.

Alemtuzumab is directed against the CD52 molecule, which is expressed on all lymphocytes, of both B-cell and T-cell lineage, thus causing a profound lymphopenia. A single dose, usually 30 mg, is all that is required.

The profound lymphopenia that is seen immediately after these antibodies are used gradually recovers over the next 3–6 weeks, while the body adapts to the new organ.

It is increasingly seen that when this recovery occurs, the percentage of Treg cells is increased and may be the mechanism by which the graft is protected.

The use of these two antibody preparations have been well tolerated without the cytokine storm that used to accompany the use of earlier antilymphocyte antibody preparations (ATGAM, OKT3, and MALG) resulting from cell death. Induction therapy with lymphocyte depletion prior to engraftment has resulted in some of the

lowest acute rejection rates, known in clinical practice of multi-organ transplantation, and is regularly used in kidney transplant.

The flip side of powerful immunosuppression is always an increased risk of infection. While this risk has been considered worthwhile in the case of multi-organ transplant like pancreas-kidney and multivisceral transplants, there is reluctance to use these drugs in liver transplantation.

The largest experience of induction using antilymphocyte drugs, thymoglobulin and Campath, has been at Pittsburgh, [25] in Starzl's clinical trials of 'tolerogenic immunosuppression'. The use of alemtuzumab for induction followed by tacrolimus monotherapy was shown to be successful in achieving steroid-free maintenance immunosuppression and an overall reduction in the burden of medication.

10.10 Pathology of Rejection Following Liver Transplantation

While it has been traditionally believed, and taught, that liver is 'resistant' to rejection, it is important to realize that 20–40% of patients experience one or more episodes of acute rejection that are clinically relevant and require additional immunosuppression [26]. In comparison, acceptable rates of acute rejection in kidney transplantation are usually below 15%.

The target of host immunologic attack is the portal triad. Typically, at first glance under low power, the expansion of the portal triad and the increased 'blueness' of the biopsy in the H&E stain are evident as lymphocytes enter and expand the portal triad. Within the portal triad, it is the cluster of bile ductules that show features of inflammation and infiltration by lymphocytes. Less commonly, the portal vein in the triad will show features of 'venulitis'.

Portal inflammatory infiltrate is comprised of a mixed population of cells: lymphocytes (T-cells, mostly), 'blast' cells, neutrophils, and eosinophils in varying proportions [26]. It is important to recognize this, as a pure mononuclear infiltrate may be more indicative of disease recurrence in autoimmune hepatitis, or viral hepatitis as was commonly seen in hepatitis C patients in the era prior to the availability of 'direct acting antiviral' drugs.

The most important and common differential diagnosis for the surgeon in the early post-operative period is to distinguish bile duct obstruction from acute rejection. Mistakenly treating biliary complications with heavy doses of additional immunosuppression can have catastrophic consequences.

Imaging to look for biliary obstruction can be done prior to proceeding to biopsy, thus helping with the differential diagnosis. However, at histopathology, bile duct obstruction is characterized by bile duct proliferation, presence of bile plugs, and neutrophilic infiltration rather than lymphocytic infiltration of the bile ducts. There will also be a lack of venulitis of the portal vein radicals, seen only in rejection and not in bile duct obstruction [27].

Important also in guiding therapy is the classification of acute rejection into mild, moderate, and severe. Banff criteria have been laid out for the diagnosis, but briefly this can be described as:

- Mild: rejection in some portal triads.
- Moderate: rejection in most or all triads.
- Severe: features of vascular involvement in the form of portal venulitis or central venulitis, in addition to the portal triad expansion and bile duct findings seen in pure cellular rejection.

Diagnosis of late acute rejection—after 3 months—is difficult, and the differential diagnosis is more nuanced requiring interpretation by an expert pathologist. Typically, in such cases, infiltration by lymphocytes and inflammation around central vein may be a prominent feature on biopsy.

Antibody-mediated rejection is also being increasingly recognized in early and late graft injury. The criteria for diagnosis of ABMR in the liver are difficult. Extrapolating from the experience of ABMR in kidney transplantation, this diagnosis may require the use of special staining for C4d deposition in the vessels and presence of circulating donor-specific antibodies in the serum [26].

10.10.1 Chronic Rejection

Prevalence is estimated at 2%, and the course is indolent, rarely presenting prior to 12 months post-transplant [26].

Obliterative arteriopathy and loss of bile ductules are the two main histological features. Early chronic rejection may have some overlap features with acute rejection, but a prominence of vascular findings, with central vein involvement and ductopenia in more than 50% of portal triads, is necessary to make a firm diagnosis.

It follows that diagnosis of chronic rejection is difficult without an adequate sample obtained by a percutaneous rather than a trans-jugular biopsy. This may prove to be difficult, especially when the patient has a prominent component of central vein involvement when the clinical presentation is like Budd-Chiari syndrome, with ascites as a prominent feature.

10.11 A Survey

Major liver transplant centres in India were approached to participate in a detailed survey outlining immunosuppression protocols, followed at their centres, and to share their institutional experience with immunosuppression and infection prophylaxis in India with its unique environment and challenges.

Those who responded are listed as contributors (see Acknowledgement section in this chapter), and their practical experience is summarized below.

The collective experience of the contributors covers a period of over 20 years and exceeds 10,000 liver transplantations performed in India since the late 1990s.

10.12 Induction Therapy (Routine Cases)

DDLT

– Methyl prednisone: Methyl prednisone was the most commonly used induction medication.[i–x] Doses used varied.
  - Weight based dosing: usually 10 mg/kg.
  - Maximum dose administered: 500 mg[ii] to 1000 mg depending on body weight.[i,iii,iv,v,vi.vii.viii.ix]
  - Timing: Anhepatic phase[i-x] usually given towards the end of anhepatic phase, just before reperfusion of the graft. Completing the administration before clamping the IVC for implantation of the allograft was specified.[vii]

LDLT

– Methyl prednisone: As in DDLT, methyl prednisone at the end of anhepatic phase and prior to reperfusion is used.[i-x]
– Basiliximab: In one centre, basiliximab induction therapy, given on post-op day 1 and 5, has enabled steroid-free immunosuppression induction,[i] with improvement in the metabolic profile [28].

10.13 Maintenance Therapy (Routine Cases)

DDLT

– Steroid: Steroid taper protocol was followed by all centres, though the exact regimen (doses used, and duration over which the taper was conducted) would vary.
  - Typically, methyl prednisone 5 mg/kg[i] or prednisone 20 mg[ii] would be given on day 1, followed by a gradual taper over 3 months, when the steroid would be discontinued. Reduction in prednisone dose by 2.5 mg every 3 days was a common protocol.[i,-x]
  - Slowing down the taper is done in cases in whom there was a rejection episode. In this situation, the taper would be resumed after transaminase levels returned to normal and stayed normal for 2 weeks.[vii]
  - Long-term steroid maintenance was used in patients with autoimmune hepatitis/cirrhosis (AIH) and primary sclerosing cholangitis (PSC),[ii] at a dose of 5 to 7.5 mg QD lifelong.[vi]
– CNI: The calcineurin inhibitor of choice was Tacrolimus.[i,-x] Again tapering doses were employed, based on drug levels and the duration post-transplant.

- Up to 3 months: 7–10 ngm/mL
- 3–12 months: 6–8 ngm/mL
- Over 12 months: 5 ngm/mL
- In patients with neurological conditions, where it was thought desirable not to use tacrolimus (especially posterior reversible encephalopathy syndrome, or PRES), cyclosporin (Neoral) use was recommended, starting at 50 mg po BID and going up to 200 mg po BID. Levels were monitored using C_0 levels, with a target value of 200–250 ng/mL, or a C_2 level of 800–1000 ng/mL.[vi,vii]
- Patients requiring a very high dose of tacrolimus to achieve/maintain adequate drug levels, defined as >10 mg po QD, may be investigated by doing 'tacrolimus genotype'. Patients identified to be 'high metabolizers' would be offered a switch to cyclosporin in view of cost constraints in this subpopulation of patients.[vii]
- The use of Neoral in diabetics, as the CNI of choice, has been advocated.[ix]

– MMF: The use of triple drug immunosuppression with Tac/MMF/Prednisone is the standard protocol at most centres.
– mTORi: Everolimus was the preferred mTORi medication employed in the following situations:

- HCC: It was usually started 1 month after transplant and low-dose tacrolimus continued.
- Renal dysfunction: In these patients, tacrolimus would be discontinued and everolimus used in place of CNI.
- In a subgroup of patients who had hyperkalaemia, even without overt renal dysfunction, switching from CNI to everolimus was considered.[vii]

LDLT

- No change from DDLT in standard maintenance immunosuppression protocol.[i, ii,iii,iv,v,vi,vii,viii,ix] Living donor recipients require less immunosuppression overall.[v]

10.14 Induction Therapy in Special Circumstances

– *Renal dysfunction*: This has been defined as low eGFR, with proteinuria.[x] Basiliximab is the favoured monoclonal antibody used in this situation, with two doses being used as per the manufacturer's recommended dosage regimen.[i, ii,iii,iv]

- This has enabled the late introduction of tacrolimus and helped preserve or reduce further damage to renal function [28]
- Strategies such as reducing nephrotoxic drugs, careful renal dosing of all medications, and avoiding cross-clamping the IVC at the time of implant have been advocated to reduce risk of exacerbating renal injury at surgery.[x]

– *'Very sick patient'* (high MELD/CTP score): Methyl prednisone was still the favoured induction agent in such patients with the dose being reduced to 5 mg/kg.[i,ii,iii,iv, viii,ix,x]
– *Recent infection* (pre- or immediate post-op): Methyl prednisone at induction, with dose reduced to 5 mg/kg[i,ii,iii,iv] with lower dose and lower target levels of tacrolimus.[i-x]

  • Basiliximab is also found useful in this situation,[i] with the delayed introduction of tacrolimus after post-op day 3 to 5[i].

    Note:

    There was no change in induction therapy protocol in renal dysfunction and patients with high MELD/CTP scores in more than one centre.[iii,v,vi,vii]

    No centre reported using a lymphocyte-depleting antibody like ATG, as induction therapy in any circumstance/protocol, and the use of non-depleting antibodies, like the anti-interleukin monoclonal antibody basiliximab usage, was limited to special circumstances. This not only could represent the need to minimize the burden of medication costs on a routine basis but also reflects the experience that infection-related patient morbidity and mortality are a greater problem in India than early graft dysfunction, due to innate or adaptive immune mechanisms.

10.15 Maintenance Therapy in Special Circumstances

– *Poor renal function*: The crucial issue here is the difficulty in differentiating hepatorenal syndrome from acute kidney injury or acute on chronic kidney injury, all of which can have a very different course, usually diagnosed for certain only on close observation after liver transplant, because renal biopsy is usually not an option in coagulopathic patient pre-transplantation.

  • Common strategies included:

    The use of basiliximab with delayed introduction of CNIs[i,ii,vi,vii,x].

    Delayed CNI introduction—after 48–72 h and at low dose—while using MMF and steroids, is widely practiced.[ii-x]

    – Long-acting formulation—Advagraf has been tried[i].
    – To determine whether immunosuppression modification is needed in this situation, eGFR is advocated in one centre, with institution of a standardized renal sparing protocol in case eGFR is >40 and <60 mL/min/1.73 m^2. This includes minimization of CNI with the introduction of everolimus, with the aim of withdrawing CNI in 6 months post-transplant.[x]
    – If CNI is not tolerated by the kidneys, switching from CNI to mTORi—everolimus—is widely practised,[i–x] with an approach to identifying chronic renal disease described above.

– *Hepatocellular cancer*: With one exception,[ix] there was a general agreement on starting mTORi in these patients, usually between 4 and 6 weeks for its anti-tumour effect.[i,ii,iii,iv,v,vi,vii,viii,x]

  • While everolimus was used in most centres, one centre reported the use of sirolimus.[x] Continuing low-dose tacrolimus was favoured, to reduce the risk of early rejection, which could require increasing immunosuppression.

– *Recent infection*: There was a general agreement on withholding MMF in this situation. Tacrolimus and prednisone as maintenance were favoured and MMF (re)introduced late, after infection was controlled/eliminated.[i,ii,iii,iv,v,vi,vii,viii,ix]

  • In the case of infection with multidrug resistant organisms, maintenance immunosuppression with steroid only was favoured, introducing CNI only after infection was controlled/eliminated.[ii]

– *Neurological dysfunction*: Switching from tacrolimus to cyclosporin in these patients was practiced in one centre, with switch back to tacrolimus after 3 months if the neurological situation improved and stabilized.[iii]
– *Early graft dysfunction*:

  • *Primary nonfunction*: The definition of primary non-function used was AST > 3000 IU/L, with one of the following: INR > 2.5, serum lactate>4, arterial pH < 7.3.
    In centres doing mainly LDLT, classic PNF was rarely or never encountered. No change in immunosuppression was the strategy favoured.[i,ii,iii]
  • *Small for size syndrome* (see below for more details):
    It was uncommon to change immunosuppression protocols in this situation. Sepsis, a common accompaniment of this situation, is to be ruled out,[iii] with reduction in immunosuppression by withholding MMF and reducing Tac levels to 2to 5.[v]

– *Autoimmune disease*: Long-term maintenance steroids are used.[ii]

10.16 Infection Prophylaxis

– Antibiotic choice and duration: Piperacillin +tazobactam, for 3 days, and stop if the cultures are negative.[i] Teicoplanin × 5 days or single dose vancomycin at induction was reported, in order to enhance Gram-positive coverage by one centre.[vi] Discontinuing teicoplanin after removal of central lines, but continuing the pip-tazobactam till 72 h, by which time the results of the immediate pre op 'pan culture' results would be available, was another strategy.[vii]

  • For patients with ACLF, ALF, 'very high' MELD, or recent infection, enhanced antibiotic, in the form of meropenem, is used and continued post-op for 7–10 days.[iii]

- Other indications for the use of meropenem included the following: re-transplantation, use of TPN pre- or post-transplantation, use of >20 units of blood/products, and use of dialysis pre−/intra−/post-transplantation.[vii] The duration of administration is determined by the clinical status of the patient and results of cultures.
- Only one centre reported using metronidazole perioperatively, in both donors and recipients.[x]

– Antifungal choice and duration: Fluconazole, until drains are removed, or till the steroid taper has brought the dose of prednisone down to 10 mg per day.[i]

- In very sick patients, those requiring transplantation for acute liver failure, or acute on chronic liver failure, or who have been dialysis dependent, those who have received multiple courses of antibiotics pre-transplant, ABOi transplantation (see below) where immunosuppression used is higher, are all considered indications for increased use of fungal prophylaxis.[vii] Anidulafungin, with the reduced chance of drug interaction with CNIs, or even amphotericin B, based on the experience with resistance of the local candida species, is used in more than one centre.[iii,ix]
- Using fluconazole up to 1 month post-transplant is not unusual,[i,ii,iii] but interference with CNI dosing is a reason to stop early,[vii] typically at 72 h.

– PCP prophylaxis: Not used by most centres [iii,iii,iv,v,vi,vii]. In cases where it was part of standard protocol, it was discontinued at 3 months.[v,x]
– CMV prophylaxis:

(a) D+/R− Valganciclovir 900 mg po QD × 3 months,[ii] although this situation is rarely encountered in Indian population.[i]
(b) D+/R+ No prophylaxis (this is the situation encountered in 99% of the population).
(c) D−/R+ No prophylaxis.
(d) D−/R− No prophylaxis.

Universal CMV prophylaxis with valganciclovir for 1 month is unusual,[iii,iv] as is selective use based on monitoring viral titres in the susceptible population (R−), with institution of antiviral therapy when the titre rises above 200copies/mL.[viii]

10.17 Rejection Management

– AST/ALT level which would trigger a biopsy: A rise above 100 IU/L,[ii,iii,iv,v,vi] or a rise more than 3 times the previous value.[i] Rarely the threshold was 10 times above normal.[v] Watching the trend rather than an absolute number was used in one centre.[x]

– Biopsy rate in the first year post liver transplant: As low as <5%,[ix] 10–15%[i,ii,iv,vii] in the majority of centres, rarely up to 20–25%.[iii,x]
  - Biopsy-proven ACR rate: 15%[x].
– Suspected ACR rate (not biopsy-proven) in the first-year post-transplant: about 25%[i.ii] to 30%[iii,iv,v,vi,vii].
  - The general principles in approach to graft dysfunction with rejection in the differential diagnosis include performing a Doppler u/s scan to look for vascular and biliary problems before proceeding to consider rejection.
  - The mainstay of management is 'pulse steroid' therapy. This could be in the form of increased doses of prednisone, or iv methyl prednisone. The use of iv methyl prednisone without biopsy proof of ACR, or where obtaining a biopsy is not immediately possible, is discouraged.[vii]

10.18 Management of ACR with Biopsy

Banff classification has been used, with mild ACR diagnosed with a score of 2/7, moderate or severe ACR with a score > 4/7[i]

– MILD ACR: Only escalation of maintenance immunosuppression is a common strategy. Using methyl prednisone iv, 500 mg QD × 3 doses, is rare.[vii]
  - Following this, a gradual steroid taper with oral prednisone is done, down to 20 mg po QD, maintaining this for at least a month after return of AST/ALT to normal range.[vii]
  - MMF is added, if patient was not on it,[ii,iii,iv] or the dose increased if the patient was on it at the time of rejection.
  - Resumption of prednisone, long term, after reversing rejection with pulse steroids, is advocated if the patient had been weaned off steroids prior to the rejection episode.[v]
– Moderate ACR: Most centres require admission to hospital with steroid pulse of methyl prednisone 500 mg to 1000 mg (depending on body weight) once daily for 3 days[i,ii,iii,iv] or up to 5 days.[i]
  - One centre reported management as outpatient with oral prednisone of 200 mg po QDx3 days.[ix]
  - Subsequent switch to oral prednisone and gradual taper as above.
  - SEVERE ACR: Steroid pulses as above.[ii,iii,iv] For patients resistant to pulse steroid therapy, one centre reports escalation of treatment to antilymphocyte preparations at first, then using the protocol for AMR,[i] with plasmapheresis, and bortezomib (see below).

If there is a good response to the pulse therapy, steroids are tapered while continuing tacrolimus and MMF or azathioprine.[i]

Using the level of AST/ALT elevation to decide between oral prednisone taper vs methyl prednisone taper was practiced in one centre.[x]

In the event that tacrolimus was at a level >6 ng/mL when the rejection episode occurred, or if the response to therapy has been slow, addition of everolimus has been used.[i]

10.19 Management of ACR Without Biopsy

Practical considerations require this to be done at times, although this practice is discouraged.

- Increase in steroid doses used empirically varies from no empirical pulsing[ii] to the use of a single pulse of methyl prednisone 500 to 1000 mg before proceeding with biopsy.[i]
- Increase or addition of MMF: Yes, provided the WBC and platelet counts are in acceptable range.[i,ii,ii,iv]
- Increase CNI only, without empiric steroids: Yes, if the level of tac at the time of suspected rejection was <5 ng/mL.[i]

10.20 Steroid-Resistant Rejection (ACR)

This has been managed with escalation of steroid-based immunosuppression in all centres.

Adding ATG (thymoglobulin) in 50 mg daily doses to a maximum total dose of 150 mg was also used, albeit not commonly.

Failure to respond would initiate management as for AMR.

Given the risks associated with heavy immunosuppression, occasionally a ‘wait and watch’ policy is instituted after the standard ‘severe ACR protocol’, with no additional treatment.[ix]

10.21 Antibody-Mediated Rejection (AMR)

Experience with AMR is limited, as is the experience worldwide. One centre reports having seen AMR only in paediatric liver transplant[iii] or only in the context of ABO incompatible transplant.[x]

Plasmapheresis and IVIG constitute the mainstay of management, especially in the context of ABO incompatible transplant, monitoring titres till they drop below 1:64.[x]

With ABO compatible or identical transplant, escalation of therapy is required, starting with ATG, and if there is no response, then proceed to plasmapheresis × 3 sessions.[i] The use of IVIg in this situation may also be required.[i]

Bortezemib has rarely been used in those patients who do not respond to the above, in a dose of 2 mg SQ on day 0, 4, 8, and 11, to a maximum of four doses.[i]

10.22 Chronic Rejection

Encountered rarely, the management strategy used[i,x] is:

- Continue tacrolimus; add everolimus with a target level > 8.
- Add MMF or Azathioprine, monitoring the WBC and platelet count.
- Continue steroids.

10.23 Graft vs. Host Disease

This has been encountered, albeit rarely, and managed with escalation of immunosuppression with pulsed steroid and increase in the dose/level of tacrolimus.[ii]

In adults, mortality is high, with paediatric age patients more likely to survive.[iii]

10.24 Passenger Lymphocyte Syndrome (Alloimmune Haemolysis) Encountered

No change in immunosuppression is advocated in this situation, which usually gradually reverses over 3–4 weeks.

10.25 Retransplant for Immunological Reasons

Retransplant is much more commonly done for non-immunological reasons, with one centre reporting 11/18 retransplantations being required for hepatic artery thrombosis or unspecified early graft dysfunction.[x] Retransplantation for immunological reasons is rare[i,x] and is more commonly for chronic rejection or recurrence of autoimmune hepatitis.[i,iii,x]

10.26 PTLD Encountered

Few patients reported[i.ii.iii] with uniformly poor prognosis.

10.27 Other Cancers Encountered

Skin cancer, haematological malignancies, and polycythaemia have been encountered.[i] Oropharyngeal, lung, and colon cancers[iii,ix] and brain, pancreas, and prostate cancers[x] have been reported.[x]

Cancers are seen to occur after a median follow-up of 42 months post-transplant.[x]

10.28 Tolerance Encountered (Withdrawal or Significant Minimization of Immunosuppression)

Yes, rarely,[i] and usually by patients withdrawing immunosuppression on their own. Withdrawal of immunosuppression under supervision was not reported from any centre.

'Operational tolerance' encountered was defined as requiring tacrolimus 0.5–1 mg per week and Myfortic 180 mg on alternate days.[x]

10.29 ABO Incompatible Liver Transplant

Majority of the centres contributing to this experience are doing ABO-incompatible liver transplants. In these,[i,iii,v,vii,viii,ix,x] the experience is summarized below:

Cut-Off titre above which you would not consider desensitization:

- A high titre at initial measurement would perhaps be a marker for failure of desensitization. No cut-off was specified by most centres in answering this question, but one centre specified a cut-off of 1:32,[vii] and multiple centres were willing to enter patients into their protocol even with a titre equal to or >1:512.[i,viii]
- The highest reported titre successfully managed, to bring it down and proceed to transplant, was 1:4084.[v]

Target Titre of desensitization regimen:

- IgG: This is variable with the reported target IgG=/< 1:32,[i] 1:8,[iii,iv] 1:16,[x] and 1:64.[v]
- IgM: 1:32,[i] 1:8,[iii,iv] and 1:16.[vi,x]

Desensitization regimen:

- Typically, this would be started 1–3 weeks before the date of transplant (LDLT) with the first dose of rituximab being administered.[v,x]

– Plasmapheresis + rituximab 300 mg, one to two doses[(i)] with MMF (1–1.5 G/day) started 1 week prior to the planned date of transplant[(v)] is another common approach.
– The goal of therapy was to bring the antibody titre to 1:16 or less. Glycosorb immunoadsorption on the day before transplant (following prior rituximab) has been used.[(viii)]
– The use of IVIg (up to 40 gm)[(vi)] during anhepatic phase and on the first post-op day, if the titres were 1:64 or higher, was practiced in one centre.[(v)]
– Monitoring of CD20 cell count was reported.[(vi)]

Induction agents in ABOi liver transplant:

– As these patients are usually LDLT, the standard protocol followed for LDLT[(i,iii,v,vii,viii,ix,x)] was commonly used, with one centre using rituximab 100 mg iv at induction.[(vii)]

Maintenance meds, different from routine transplant:

– Some centres reported using immunosuppression no different from standard protocol but with Tac levels rigorously monitored to maintain levels at the high end of the acceptable range.[(i,iii,v)]
– Others advocate using intravenous methyl prednisolone, given at the dose of 2 mg/kg for the first week and then 1 mg/kg for the second week. Introduction of oral prednisone is delayed to 10–12 days post-transplantation, and later a gradual taper (10 to 20 mg per day) was followed till a maintenance dose of 20 mg per day[(vii)] or 30 mg/day.[(vi,vii)]

Antibody titre monitoring protocol:

– Considerable variation in monitoring protocol was noted. A frequent approach is to monitor daily for 1 week[(iii)] or 2 weeks[(vii)] and on alternate days for 2 to 4 weeks and, thereafter, once a week for 1 month and once in 2 weeks for 2 months,[(vii)] that is, until 3 months were completed post-transplantation.[(vii)]
– A less intensive antibody titre matching schedule was also reported, with antibody titres weekly[(i)] or twice weekly[(iii)], only for the first month post-transplantation.
– After 3 months: No further antibody checks[(I,iii,vii)] or at monthly or 3 monthly intervals for up to 1 year.[(vii)]

10.30 Comments From Experience

– *Antibodies*: The use of basiliximab helped in managing patients with renal dysfunction, as CNI could be withheld for up to 3 weeks.
  • Anti-thymocyte globulin (ATG, Thymoglobulin) was never used for induction but was used for the management of steroid-resistant ACR in doses of

2.5 mg/kg[ii] or a standard dose of 50 mg daily.[i] To monitor the ATG, the target neutrophil count was kept >2000 and the platelet count >75,000. The lymphocyte count was also monitored, and the dose of ATG increased if the lymphocyte count was >50/μL, or if it refused to drop with the low-dose ATG strategy.[i,ii] The maximum total dose was limited to 150 mg.[i]

– *mTORi side effects*:

  (a) Hyperlipidaemia: This was a frequently encountered side-effect with this group of drugs.
  (b) Pulmonary toxicity: Encountered rarely but has been considered the cause of death[i] in rare instances.

  Proteinuria is universally encountered with everolimus, and there is an increased incidence of incisional hernias. Oral ulcers may occur rarely.[i]

– MMF

  (a) Platelet count cut-off for starting MMF: >20,000,[viii] >25,000,[i] but most want >30,000.
  (b) GI side effects: This has not been a major problem and can be easily managed with a total dose of MMF <2000 mg/day.[i] Switching to Myfortic is a popular strategy.[viii]

– *Azathioprine*: This is a good drug and a viable alternative when long-term medication cost considerations require.[i,v,ix] The allograft liver tolerates azathioprine well.[i,v,ix] Most contributors, however, said they had no experience with azathioprine in the context of liver transplantation.
– *Non-compliance*: This was encountered rarely and estimated to be only about 2–3% of cases.[viii] More common in alcoholics,[i,ii] in young patients,[i] and in transplants done for acute liver failure, especially with Ratol poisoning.[i]
– *Renal dysfunction*: While delaying immunosuppression for up to 5 days is possible,[v] this was only being done in a few centres, with all others reporting the use of basiliximab, to be able to safely postpone introduction of tacrolimus.

  • The use of urine protein-creatinine ratio (UPCR) on a spot check was emphasized as an important monitoring tool for diagnosis of chronic kidney disease (ratio > 0.3), in which case everolimus use would be instituted, with reduction of CNI. Persistent elevation of UPCR, further confirmed by 24-h urine protein estimation, would constitute a reason for referral to nephrology for the management of chronic kidney disease.[vii]

– *Infection*

  • During acute infection, Tac and MMF are stopped.[i,ii] Requirement of fluids for resuscitation or hemodynamic instability are indications for hydrocortisone: (50–100 mg iv Q 8 hourly), with re-introduction of tacrolimus once the sepsis improves.[I,vii]
  • Bile leaks: Since this is more common in LDLT, maintaining these patients on low-dose tacrolimus and steroid is used with frequent monitoring to detect rejection early.[ii]

– *HCC*
  - The dose of tacrolimus is kept low at <3 ng/mL[(i)] and everolimus added after the first month[(i,ii)] with a target level of 5 to 6 ng/mL.[(i)]
– *PNF*: The definition used is that of UNOS,[(i)] with continuation of the standard protocols of immunosuppression.[(vii)]
– *SFSS*: This is diagnosed[(i)] in the setting of a graft that has a GRWR of <0.8, with the presence of two of the following during the first post-operative week, after excluding vascular, infection, and immunological causes of graft dysfunction:

  (a) Total bilirubin >5 mg/dL
  (b) INR >2
  (c) Encephalopathy grade > 3, with refractory ascites

  No change from the standard immunosuppression protocol[(vii)]
– *ACR*: Details of the management have been outlined above, and there is a broad agreement on strategies, with the effort to manage with steroid pulses, and slow taper, and reserve use of antilymphocyte preparations to the severe cases which on repeated biopsies show persistent rejection with or without C4D staining positivity.
– *AMR*: The difficulty of diagnosing this as a distinct entity was emphasized, with no fixed protocol for change in strategy from severe ACR above.
– *Chronic rejection*: This again is not managed with a predetermined protocol in most centres, although there is a broad agreement on switching to everolimus and reducing the other drugs the patient is on to minimize the risk of opportunistic infections[(vii)].
– *GVHD*: When encountered, this is treated with increasing the steroid and CNI doses. No change or even reduction in immunosuppression has been done,[(viii)] perhaps because of poor outcomes in this situation.[(ix)] Opportunistic infections when encountered in this situation have a very poor prognosis.
– *Passenger lymphocyte syndrome*: As with GVHD, the approach has been minimalistic.[(ix)]
– Re-transplant: Is usually managed with the standard immunosuppression protocols.

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Appendix

Questionnaire Circulated to Liver Transplant Centres in India

Practical Immunosuppression in Liver Transplant: Experience of Experts in India

Name of the Centre:
Chief Surgeon:
Hepatologist:

Standard Induction

DDLT

– Medication and dose (fixed or weight based)
– Timing

LDLT

– Medication and dose (fixed or weight based)
– Timing

Change in standard induction (if any) with:

– Renal dysfunction
– Very sick patient (High MELD/CTP score)
– Recent infection

Use of antibodies in induction:

– Basiliximab: Yes/never/selectively
– ATG: Yes/never/selectively

(If 'yes', or 'selectively' for above question, please elaborate in comments section below)[1]

Standard Maintenance

- Medication list
- Steroid taper protocol
- Choice of CNI
- Target CNI levels
- mTOR inhibitors

  Different strategy in *deceased donor* vs *live donor* transplant: Yes/no
  (If yes, please delineate in the comment section below)[2]
  Different strategy in renal dysfunction: Yes/no
  (If yes, please elaborate in comments below)[3]
  Change in maintenance with infection pre- or immediate post-tx: Yes/no
  (Please comment below)[4]
  Change in maintenance immunosuppression with HCC: Yes/no
  (Please comment below)[5]
  Change in immunosuppression with early graft dysfunction (EGD)

- Primary non-function (PNF): Yes/no

  (Please delineate in the comments section below)[6]

- 'Small for size' (SFSS): Yes/no

  (If yes, please outline in the comments section below)[7]

- Any other reason: Yes/no

  (If yes, please outline in the comments section below)[8]
  Infection Prophylaxis

- Antibiotic choice and duration:
- Antifungal choice and duration:
- PCP prophylaxis:
- CMV prophylaxis and duration
- D+/R−
- D+/R+
- D−/R+
- D−/R−

Rejection Management

AST/ALT level which would trigger a biopsy:
Biopsy rate in first-year post liver transplant:

Suspected acute cellular rejection (ACR) rate in first-year post-transplant:
Management of acute rejection *with biopsy*:

- Mild ACR
- Moderate ACR
- Severe ACR

Management of suspected acute rejection *without biopsy*:

- Steroid doses used empirically:
- Increase or add MMF: Yes/no
- Increase CNI only without empiric steroids: Yes/no

Steroid-resistant ACR encountered: Yes/no
(If yes, please outline strategy in the comments section below)[9]
Acute antibody-mediated rejection (AMR)encountered: Yes/no
(If yes, please discuss management strategy in acute AMR in the comments section below)[10]
Chronic rejections encountered: Yes/no
(If yes, please outline management strategies in chronic rejection)[11]
Graft vs host reaction encountered: Yes/no
Passenger lymphocyte syndrome (alloimmune haemolysis) encountered: Yes/no
(If yes, please delineate the immunosuppression strategy in this situation)[12]
Retransplant required for immunological reasons: Yes/no
(If yes, please discuss in the comments section below)[13]
PTLD encountered: Yes/no
Other cancers encountered: Yes/no
If yes, what were they?
Tolerance encountered (Withdrawal or significant minimization of immunosuppression): Yes/no

ABOi Liver Transplant

- Cut-off titre above which you would not consider desensitization:
- Target titre of desensitization regimen:
- IgG
- IgM
- Desensitization regimen:

Induction agents in ABOi liver transplant:

- Agent and dose

Maintenance meds, different from routine transplant: Yes/no
Antibody titre monitoring protocol

- Up to 3 months:
- Beyond 3 months:

General Opinions Based on Experience with Immunosuppression Agents in India

Preferred CNI and why:
Preferred mTORi and why:
Is hyperlipidaemia a problem with mTORi?
Is pulmonary toxicity a problem with mTORi?
Platelet count cut-off for starting MMF:
GI side effects of MMF, is it a problem?
Experience with azathioprine:
Non-compliance. Is it a problem?
Any other comments or experience you would like to share:

Comments/Important Experience Requiring to Be Shared

1. Use of antibodies in induction
2. DDLT vs LDLT maintenance therapy
3. Change in maintenance therapy with renal dysfunction
4. Change in maintenance with recent infection
5. Change in maintenance with HCC
6. PNF (please comment on definition of PNF that you use)
7. Small for size (SFSS)
8. Other reasons to change maintenance immunosuppression
9. Steroid resistant ACR. Management strategy
10. AMR management strategy
11. Chronic rejection management
12. GVHD and passenger lymphocyte (alloimmune haemolysis) syndrome
13. Re-transplant

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Chapter 11
Advances in Gastrointestinal Surgery

T. K. Chattopadhyay

11.1 Non-Operative Treatment of Adhesive Small Bowel Obstruction: Does It Need a Rethink?

Adhesive small bowel obstruction (ASBO) is the most common complication of a laparotomy done for any reason. The obstruction thus produced can be seen in the immediate postoperative period in the short term or years later in the long term. Thus, patients have a long-term risk of ASBO. The episodes are not infrequent and are recurrent, interfering in the day-to-day lives of the patients. More importantly, these episodes may force the patients to seek hospital admission, with loss of work and financial burden. The magnitude of the problem can be appreciated from the reports published by Sikirica et al. [1] and Ray et al. [2] They reported over 3,50,000 operations performed annually in the USA for SBO, which incurred 2.3 billion dollars in expenditure. Of these, nearly three-fourths of the cases are due to ASBO [3].

Conventionally, all ASBO patients are managed non-operatively, because it is believed that operative treatment can lead to further adhesions, resulting in more episodes of obstruction. Based on this premise, non-operative treatment had been the rule for decades. It is true that nearly 80% of patients of ASBO get spontaneously resolved with this policy [4–6]. But the problem is it recurs. It recurs because the causative factor remains. When called upon to manage such patients, surgeons face a dual problem: non-operative management, even if it becomes successful, will leave behind the adhesion, and operative treatment will form new

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adhesion(s). Both strategies will cause recurrent obstruction. The question is which of the two has higher recurrence rate. A number of studies done in the past have suggested that non-operative treatment has higher propensity of recurrence [7, 8]. A recent population-based retrospective study conducted in Ontario, Canada, has also shown similar result [9]. The pertinent findings of this study are discussed here.

The authors of this study collected data of all patients admitted with the first episode of ASBO in Ontario city hospitals between 2005 and 2014. They included 27,904 patients. They divided patients based on operative and non-operative treatments. The primary outcome of the study was to ascertain recurrence rate of ASBO following operative and non-operative treatment. The secondary outcome was to detect additional ASBO after the second episode for which they followed all patients for a maximum of 10 years. Over 22% of patients were managed with surgical treatment, and the remaining were non-operatively treated. When the patients were followed, they reported reduction of surgical treatment on their second and third episode of ASBO to 16.6% and 11.8%.

With reference to the primary outcome measure (i.e. recurrence rate)—they reported that operatively managed patients had lower recurrence than those treated non-operatively (13% vs 21.3% with p value <0.001). Even the 5-year post-treatment recurrence was lower in the operatively treated patients than in the non-operatively treated patient (11.2% vs 19.2%; $p < 0.001$). As for the secondary outcome of additional recurrence, the authors showed that the non-operatively managed group was associated with increased recurrence rate varying between 19.2% following the third episode. In addition, surgical treatment during any of these situations brings down the 5-year probability of recurrence (19.2% with surgical treatment vs 39.2% with non-operative treatment).

Clearly, the study amply shows that operative treatment for ASBO significantly reduces the recurrence rate. True, after any form of therapy including surgery, recurrence is a genuine problem, but the disease course is altered for the better with surgical treatment. While lamenting on the positive outcome of surgery in this study—current strategy of initial non-operative treatment is still valid. Even in this study, surgery was done in 20% of cases only. Only when this fails to resolve, operative treatment should be seriously considered. Other positive aspect of their study is, it outlines disease trajectory of ASBO on the long term—natural history of the disease. This study shows that recurrence is quite common in ASBO, and each recurrent episode increases the risk. Operative management appears to reduce both of these. A point to consider is avoiding surgery altogether during the first episode does not take care of the potentially recurrent nature of ASBO with all the risks involved along with financial burden. It is also to be emphasized that the disease may be benign but has debilitating impact on the health of the patient, and hence, patients are to be taken on board through discussion to avoid unwarranted unpleasantness.

11.2 Definitive Chemoradiotherapy for Oesophageal Carcinoma

Surgery has been the mainstay for the treatment of patients with oesophageal cancer for a long time. This has given good results in a select group of patients. The operation itself is complex and associated with morbidity and some mortality. Researchers have been looking for an alternative but equally effective form of treatment as surgery. One such alternative is definitive chemoradiotherapy (DCRT). There is evidence that DCRT provides results that are not inferior to surgery. In this section, we review the work in this area.

One of the first studies on DCRT was published way back in 1992. Herskovic et al. [10] did a randomized study in localized oesophageal cancer comparing DCRT and only radiotherapy. They included both squamous cell and adenocarcinomas (mostly squamous cell). They showed an improved 5-year survival with DCRT (26%) versus RT alone (0%) with a median survival of about 12 and 9 months, respectively.

Similar results have been reported in other studies also [11, 12]. Various studies have identified some prognostic factors. These are:

1. Histological type (squamous cell or adenocarcinoma): Smit et al. reported a 2-year survival following DCRT of 29% in patients with squamous cell (SCC) and 17% in those with adenocarcinoma (AC) [13].
2. Stage of the disease: Stage I disease in SCC has been reported to have a 3-year survival of 42% as compared to 25% and 16% in stage II and III, respectively, following DCRT [14]. Even in AC, the stage of the disease has been shown to be an important prognostic factor of response to DCRT [15]. In these patients (with AC), recurrence is particularly high (55% in 22 months of follow-up) even after complete response, which is attributed to advanced T-stage and node positivity [16].
3. Proximal location of the tumour in SCC has a bad prognosis after DCRT with a 3-year survival of only 25% [17].

It is thus clear that DCRT does work. Is it better than or comparable to surgery? A number of studies are available that compared DCRT and surgery for oesophageal cancer.

In 2020, Morgan et al. [18] compared DCRT, surgery alone and neoadjuvant chemotherapy, followed by surgery (CTS). They included 417 patients, of which 173 received DCRT, 126 received surgery alone and 118 received CTS. There were no 30-day or 90-day deaths in the DCRT group. Patients who underwent surgery alone had 7.9% 30-day and 9.5% 90-day mortality. In the CTS group, it was 0.8% and 5%, respectively. Therapy-related toxicity was seen in 39.3% following DCRT and 60.2% following CTS, respectively. All these patients were followed up for at least 5 years or until death. The median survival was 22 months in DCRT, 30 months in surgery alone and 22 months in the CTS group ($p = 0.42$). Similarly, the 2-year

survivals were 44.3%, 56.2% and 42.4% in the three groups, respectively. This difference too was not statistically significant ($p = 0.4$).

Motoori et al. in 2012 [19] published the first study comparing results of radical oesophagectomy and DCRT in early SCC of the oesophagus (T1bN0M0). They treated 71 patients with DCRT and 102 patients with radical surgery. One patient in the DCRT group died due to radiation toxicity (pneumonia). No patient died following surgery. Disease recurrence was seen in 20 of 71 patients in the DCRT and in 12 of 102 in the surgery group. The progression-free survival at 3 and 5 years were 62% and 60.6% in the DCRT and 83% and 73.8% in the surgical group, respectively ($p = 0.12$). The overall survival, at 3 and 5 years, was also not statistically different in the two groups, being 77.8% and 68.6% in DCRT and 87% and 77.7% in surgery group ($p = 0.115$).

Long-term survival has also been evaluated in a randomized study from Hongkong, comparing DCRT and surgery alone in resectable oesophageal cancer [20]. The authors of this study included 81 patients (36 in DCRT and 45 in surgery alone arm). Post-treatment mortality of 6.8% was reported in the surgery group. The morbidity was 67% in DCRT and 38.6% in those undergoing surgery. Both the 5-year overall survival (80% in DCRT and 29.4% in surgery group; $p = 0.15$) and 5-year disease-free survival (47.2% in DCRT and 25% in surgery arm; $p = 0.07$) were comparable. Even the mean time to recurrence was comparable in the two groups (525.7 days in DCRT and 481.9 days in the surgery group).

In 2018, a meta-analysis was published comparing DCRT and surgery [21]. This too has shown a similar 2- and 5-year overall survival in the two groups, even on a stage-wise analysis. Patients with lymph nodal metastases tended to fare better with DCRT than surgery, even though the difference was not statistically significant. The 5-year progression-free survival was also similar in the two groups. One observation in this meta-analysis was that Western patients fared worse with DCRT than Asian patients. With dose modification, DCRT can be used successfully even in patients of oesophageal cancer with compromised liver functions [22]. Thus, it is clear that DCRT is an alternative to surgery for the management of squamous cell oesophageal cancer. Its results, both in the short and long term, are at least as good as surgery [23].

Local recurrence (in the lymph nodes or in the residual oesophagus) following DCRT can be managed with salvage oesophagectomy with reasonable results [24]. Salvage surgery following recurrence after DCRT has been compared with neoadjuvant CTRT and surgery. Both mortality and complications [25] are with similar overall survival. Thus, DCRT seems to have the potential to replace surgery.

11.3 Pain in Chronic Pancreatitis

The vast majority of patients of chronic pancreatitis suffer from pain of varying intensity affecting their day-to-day life, often leading to loss of job and resultant financial distress. The commonly believed mechanism is increased intraductal

pressure caused by either stone or stricture. However, this does not seem to be the only reason for pain. Had it been so, all patients should have relief from pain following stone clearance, stricture dilatation or surgical intervention. Thus, pain in chronic pancreatitis seems to be due to factors other than pancreatic ductal hypertension [26]. Contemporary literature points to an interplay between these factors in the causation of pain in chronic pancreatitis.

1. Increased intrapancreatic ductal pressure as a cause of pain has been reported [27]. While Sato et al. [28] and Okazaki et al. [27] showed increased ductal pressure in patients with chronic pancreatitis, others failed to show it [29], irrespective of whether the patients had pain or not.
2. Increased pancreatic parenchymal pressure as a cause of pain in chronic pancreatitis has also been studied. Ebblehoj et al. [30] reported increased pancreatic parenchymal pressure in patients with painful chronic pancreatitis. However, a similar result had not been reported by another study [31]. Pain in chronic pancreatitis due to raised parenchymal pressure (due to increased fibrosis) is akin to compartment syndrome, as suggested by Fasanella et al. [32] It is possible that the raised pressure compromises blood flow. The resultant ischaemia causing acidosis may activate nociceptive receptor protein vanilloid to produce pain [33].
3. Both raised ductal pressure and parenchymal pressure produce morphological abnormality of the pancreas. The morphological changes (degree of fibrosis and atrophy of the gland) can be accurately detected by magnetic resonance cholangiopancreatography (MRCP) with diffusion-weighted imaging, as has been reported by Frokjeer et al. [34] However, the morphological changes thus detected do not correlate with pain. The observation that even after total pancreatectomy the patient may continue to have pain [35] points to factor(s) other than the pancreatic parenchyma involving the supplying nerve plexus.

11.3.1 Neurobiology of Pain in Chronic Pancreatitis

It involves three interrelated factors: (1) presence of nociceptive stimulus, (2) peripancreatic neuropathy and (3) central handling of the received stimulus.

Nociceptive stimulus through its receptor in peripheral nerve generates a pain signal. This signal travels through the afferent fibres reaching the anterior dorsal root of the spinal cord. Through the release of neurotransmitters (e.g. vanilloid-1), the signal reaches the brain and produces pain. Over a period of time, these nociceptive receptors become more sensitive to further stimuli, as a result of which not only the threshold for activation decreases but also it increases the response (pain) [36].

Following chronic pancreatitis, various forms of neuropathy occur in the pancreatic nerves and have been shown to be related to the genesis of pain [37, 38]. Lastly, there is the central processing of the transmitted nociceptive stimulus. What happens is, following receipt of these stimuli, the central neurons become

over responsive to these, manifesting with allodynia or hyperalgesia due to oversensitivity to the painful stimulus [39]. All these occur due to central sensitization. The mechanism of central processing is complex. The nociceptive stimulus from the pancreas first ascends through the afferent fibres, reaching the cortex of the brain. In the cortex, functional reorganization takes place in the pain processing areas such as the insula and cingulate gyrus apart from the somatosensory cortex. In addition to this reorganization, the neurons are rendered abnormally excitable [40].

Following central processing, the pain signals are modulated and transmitted downwards through the efferent fibres. Modulation can be both increased and decreased and is responsible for either excitation or inhibition of pain. The balance between the two is critical for pain perception. In chronic pancreatitis, abnormal descending inhibitory pain modulation has been reported [41].

When the disease is far advanced, this pain modulation does not occur, and pain persists, independent of the offending stimulus [42].

11.3.2 Pain Due to Complications of Disease

While the above factors can explain how pain originates in chronic pancreatitis, complications of chronic pancreatitis, like duodenal ileus, biliary obstruction, pseudocyst, splenic vein thrombosis and even peptic ulcer, can be responsible for the pain [26].

11.3.3 Other Causes of Pain in Chronic Pancreatitis

Patients with chronic pancreatitis have been shown to have sympathetic overactivity with resultant high catecholamine level, which lowers the threshold of pain [43]. Another hormone, cholecystokinin (CCK), has also been shown to be elevated in patients with chronic pancreatitis. CCK increases the pressure in the pancreatic duct leading to pain. It can also act through the activation of the neural pathway described earlier [44]. This observation may have clinical relevance as one study has shown amelioration of pain with the use of CCK receptor blocker [45]. A number of patients of chronic pancreatitis use opioids for relief of pain. Unfortunately, opioids can be responsible for pain due to its effects on the gastrointestinal tract, like constipation, nausea, reflux and abdominal pain [26]. Complications of surgical treatment also can cause pain due to adhesive obstruction, stricture of bile duct or pancreatic duct [26].

To summarize, to understand the mechanism of pain in chronic pancreatitis, one has to go beyond the conventional intraductal or parenchymal hypertension theory. Central processing of nociceptive stimulus in the central nervous system is equally

important. Inflammation of the pancreas and its nerves have been reported to alter pain processing, both at the spinal and cortical levels. Normally, following nociceptive stimulus reaching the cortex, pain inhibitory response travels through the descending tracts of the spinal cord. In chronic pancreatitis, there is loss of inhibitory control, resulting in hyperalgesia. In addition, other factors are also suggested in the current literature. These can be due various complications of chronic pancreatitis, like duodenal or bile duct obstruction, pseudocyst, splenic vein thrombosis, etc. Pain can also be due to the side effects of opioid drugs commonly used in chronic pancreatitis or due to the side effects of surgery, like adhesive obstruction of the bowel, injury to the pancreas or the bile duct. Sympathetic overactivity and increased levels of CCK in chronic pancreatitis have been reported. Thus, pain in chronic pancreatitis can be considered multifactorial.

11.4 Management of Cystic Tumours of Pancreas

Cystic lesions of the pancreas are increasingly detected in current clinical practice. This is attributable to the frequent use of ultrasound (US), computerized tomography (CT), magnetic resonance imaging (MRI), etc. The majority of these cysts are neoplastic with high malignant potential [46]. Therefore, one needs to formulate an effective strategy to treat these patients. It is important to identify the characteristics of each cyst, because not all cystic lesions require surgical removal. The cysts can be mucinous or serous. While serous cysts are almost always benign, mucinous cysts have a high malignant potential and hence require careful assessment.

Non-mucinous cystic tumours include solid pseudopapillary epithelial neoplasm (SPEN) and cystic variant of pancreatic neuroendocrine tumour (C-PNET). These also have malignant potential.

Thus, assessment of these lesions is extremely important for decision-making. Assessment must start with clinical evaluation, though imaging, namely, CT or MRI, is a prerequisite for diagnosis. Endoscopic ultrasound (EUS) is increasingly being used for better evaluation. EUS has the added advantage of obtaining fluid from the cyst for cytological examination and estimation of tumour markers, like CEA and CA 19-9. Even the samples for genetic study for KRAS and GNAS mutation can be obtained through EUS.

11.4.1 IPMN

This can be either main-duct or branch-duct type. Both variants have malignant potential—high for the former and relatively low for the latter. Malignancy in these cases can be either high-grade or low-grade dysplasia or frank carcinoma [47].

Main-duct IPMN on imaging is associated with dilatation of the pancreatic duct (localized or diffuse). Branch-duct IPMN, on the other hand, has been shown to be connected to the main pancreatic duct. The lesion is often polycystic [48]. The features suggestive of malignancy on imaging are:

- Size of the cyst 3–4 cm
- Presence of mural nodule
- Dilatation of the main pancreatic duct (5–10 mm or more)
- Associated pancreatic atrophy
- Concomitant lymph node enlargement
- High level of CA 19.9 in aspirated cyst fluid
- Growth in size of cyst on follow-up imaging

The suspicion is strengthened if associated with pancreatitis and/or diabetes and obstructive jaundice occurring in a pancreatic head mass [47]. In the light of all these, all patients with main-duct IPMN should undergo resection and be kept under indefinite surveillance, because long-term recurrence of these tumours can occur. On the other hand, branch-duct variety of IPMN may not necessarily need surgical removal, because many of these tumours are not as malignant, as the main-duct variants. They can be carefully followed regularly. If during follow-up the lesion appears to have grown bigger than before or has a higher grade of dysplasia or if a nodule appears, these too warrant resection.

Main-duct IPMN is known to be multifocal, and hence total pancreatectomy should be considered particularly if the patient has a family history of pancreatic cancer [49].

11.4.2 Mucinous Cystic Tumours

This is the other mucinous neoplasm. The lesion occurs commonly in the body and tail of the pancreas, in women of child-bearing age. On imaging (CT, MRI), the cyst is not associated with dilatation of or communication with the main pancreatic duct [50]. Most such lesions are symptomatic (due to pain). They do have a malignant potential, which is well correlated with the size of the lesion (>4 cm). This has a bearing on the treatment. While lesions >4 cm should be resected (distal pancreatectomy with/without splenectomy), smaller lesions can be watched with regular surveillance at 6 monthly intervals [51]. Complete removal of mucinous lesions can be considered curative, and patients need no further action.

The other cystic tumours of the pancreas are serous cystic adenoma, solid pseudopapillary epithelial neoplasm (SPEN) or cystic pancreatic neuroendocrine tumour (C-PNET).

11.4.3 Serous Cysts of the Pancreas

Serous cysts of the pancreas are almost always benign. They commonly affect postmenopausal women. Symptom(s) are related to the size of the lesion. Since, these have no malignant potential, size does not play a role in resection, which is considered only in symptomatic patients. On imaging, the lesions are polycystic in nature with calcification and satellite scar. They are usually small in size [50]. Endoscopic ultrasound-guided fine-needle aspiration is diagnostic of a serous cyst. Tumour markers like CEA or CA 19.9 are extremely low [52]. Surgery is curative, whenever it is done.

11.4.4 Solid Pseudopapillary Epithelial Neoplasm (SPEN)

Though non-mucinous, these also have a malignant potential. These can occur in any part of the pancreas. As a rule, these occur in young women. These lesions are known to attain a large size, which may cause symptoms like pain. Cross-sectional imaging (CT/MRI) showing a large well-encapsulated tumour is diagnostic. In view of the malignant potential and affecting young patients, these are best resected. Post-resection recurrence of these tumours can be a problem, and hence patients should be kept under regular follow-up [50].

11.4.5 Cystic PNET

These lesions affect both men and women equally. These tumours are usually non-functional. They are usually incidentally detected on CT or MRI which show a unilocular or multilocular cyst with a thick vascular capsule. Cyst fluid analysis of these can show high chromogranin and low CEA content, while lesions smaller than 2 cm can be observed; larger lesions >2 cm should be resected [53].

11.4.6 International Guidelines for the Management of Cystic Tumours of the Pancreas

There are three such guidelines: the Fukuoka guidelines [48], the European consensus guidelines [53] and the American Gastroenterological Association (AGA) recommendation [54]. There are subtle differences among these, be it with reference to resection, screening or surveillance. These are:

For resection: Both Fukuoka and European guidelines recommend resection if there is obstructive jaundice, size of the main pancreatic duct >10 mm, presence of a nodule >5 mm and enhancing on contrast imaging and if the cytology reveals dysplasia or frank malignancy. The American guidelines recommend resection for cytological evidence of malignancy as well as bigger tumour (>3 cm), dilated main pancreatic duct and documented nodule. Two of the latter three should be present for consideration of surgical resection along with proven malignancy.

For screening: While the Fukuoka guidelines recommend screening with EUS when the cyst wall is thick and associated with lymph node enlargement, the sudden change in the calibre of the pancreatic duct, cyst >3 cm and steady growth >5 mm in a 2-year follow-up, the European guidelines suggest screening for cysts >4 cm, presence of diabetes and growth of cyst >5 mm in 1 year. The AGA guidelines suggest EUS if the main pancreatic duct is dilated or the cyst >3 cm.

For surveillance: The Fukuoka and European guidelines advocate it both following resection and detection. The former considers the size criteria for surveillance, but the latter does not suggest surveillance beyond 5 years for stable disease. Regular surveillance for resected malignant cyst has been recommended by them.

11.5 Targeted Therapy in Gastric Cancer

Surgical resection remains the cornerstone of treatment for gastric cancer. The use of chemotherapy with or without radiotherapy used before or after surgery is aimed at better results.

Drugs used in chemotherapy are fluoropyrimidine, platinum containing agents and taxanes. The combination regimen used as the first line of treatment comprises epirubicin, oxaliplatin and capecitabine. Irinotecan and docetaxel are used as the second line of treatment. Initially, all gastric cancer patients respond to chemotherapeutic agents but soon become resistant to them. As of now, there is no biomarker which predicts chemosensitivity, and hence the agents are chosen empirically. The results of various combinations of drugs for advanced metastatic gastric cancer are poor, to say the least, most patients succumbing within 1 year.

In view of this, the focus has shifted to targeted therapies. These are aimed at the genetic mutation and signalling pathways involved in tumourigenesis and its progression. Various targeting events like mitogenic signalling, angiogenesis and immune checkpoint are being explored and evaluated at clinical trials. These are being discussed below:

11.5.1 Targeting Mitogenic Signalling

HER-2 (human epidermal growth factor receptor-2) is a common mitogenic agent in the causation of gastric cancer and overexpressed in a quarter of the patients. This gene is involved in cellular proliferation, growth, adhesion and migration. HER-2

acts in tandem with other members of the same family to which it belongs: Erb $B_{2,}$ to activate RAS- MAPK (mitogen activated protein kinase), and phosphatidylinositol 3-kinase (PI3K)–AKT pathways, in order to achieve the above functions (proliferation, growth, adhesion and migration).

Trastuzumab is an agent used in HER-2-positive gastric and oesophagogastric cancers. This drug is a humanized IgG1 monoclonal antibody with the ability to block HER-2 receptors. This in turn triggers antibody-dependent cell-mediated cytotoxicity, which stops the growth of the tumour [55]. This drug has been used in combination with cisplatin fluoropyrimidine-based chemotherapy and compared with chemotherapy alone in advanced HER-2-positive gastric cancer (phase III ToGA trial) [56]. Overall response and progression-free survival observed in this trial showed significantly better results with combination therapy than chemotherapy alone (overall response rate of 47% vs 35%, $p < 0.001$). Unfortunately, the good effect of adding trastuzumab is not long-lasting, and the response tends to wane with time. It seems this problem can be solved with the use of trastuzumab conjugated with nanoparticle albumin-bound paclitaxel as has been shown in a mouse model with HER-2-positive gastric cancer [57].

11.5.2 Targeting Angiogenesis

Angiogenesis (neovascularization) is extremely important for cancer cells not only to survive but also for proliferation and invasion. Angiogenesis occurs through multiple signalling pathways involving vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and hepatocyte growth factor (HGF), among others. These have been studied for their possible therapeutic targeting ability in various cancers. Of these, antibodies against VEGF and its receptor have been found effective when used in combination with chemotherapy [58]. VEGF and its receptor are overexpressed in approximately 30% of gastric cancers and hence are considered suitable for therapeutic targeting [59, 60]. Monoclonal antibody raised against VEGF (e.g. Ramucirumab) when given to VEGF-positive gastric cancer patients gets bound to the receptor and prevents the activation of VEGF. Ramucirumab has been found effective both as a single agent or when used in combination with chemotherapy. Bevacizumab, another anti-VEGF monoclonal antibody, is also useful when used in combination with chemotherapy. Ramucirumab has shown significantly better results when used in combination with paclitaxel than paclitaxel alone (overall survival 9.6 months vs 7.4 months, progression-free survival 4.4 months vs 2.9 months and overall response rate 28% vs 16%) [61].

11.5.3 Targeting Immune Checkpoints

Cancer cells have the ability to escape immune surveillance by the host T-lymphocytes. This is achieved through the action of programmed death ligands (PDL-1 and PDL-2) expressed on the tumours. When these are bound with their

receptors, these can depress T-cell activity and hence cause immune suppression. PDL-1 is expressed in a varying number of patients of gastric cancer ranging between 15% and 70%. Since these PDL-1 tumours have poor prognosis [62], PDL-1 can be targeted by drugs like pembrolizumab and nivolumab. They enhance immune surveillance by which they identify the escaping cancer cells and kill them. Efficacy and safety of the immune checkpoint inhibitor (pembrolizumab and nivolumab) has already been described with overall response rate of 22%, progression-free and overall survival at 6 months of 24% and 69%, respectively [63, 64]. PDL-1-positive tumours have better results than PDL-1-negative tumours. These drugs can be used singly or along with chemotherapy.

11.6 Management of Acute Necrotizing Pancreatitis

Acute pancreatitis (AP), a disease with varied aetiology, is quite common in all countries [65]. The disease can be mild, moderate or severe. The majority of patients have a mild disease (80%) with no local or systemic complications [66]. These patients make an uneventful recovery. The remaining 20% of patients can have either moderately severe or severe disease, depending on the presence of organ failure for <48 h or beyond [67]. These patients have a higher mortality (about 25%) [68]. In severe acute necrotizing pancreatitis (ANP), more than 30% of the pancreas is necrosed as determined by image analysis. Such patients commonly have associated fluid collections in and/or around the pancreas. When fluid collections occur without solid material in it (necrotic tissue), the condition is referred to as acute fluid collection (AFC), occurring within 4 weeks of onset of pancreatitis. When it occurs after 4 weeks and is associated with a wall, it is called a pseudocyst. Similarly, when fluid collections occur following necrotizing pancreatitis and contains both fluid and necrosed material, it is called an acute necrotic collection (ANC). The same ANC after 4 weeks matures and has a thick wall formed and is then called walled-off necrosis (WON). These collections may remain sterile or get infected. The presence of infection is ominous. While sterile necrosis has a lower mortality (5%–10%), infected necrosis has a high mortality (20%–30%) [69]. This is why every effort must be made to detect the presence of infection early in ANP. A contrast-enhanced CT scan can do it in most instances. A word of caution—the CT scan should be done after the first week of illness, because the necrosis may not be evident early in the course of the disease. When present, the necrosis may be noted both inside and outside the pancreas. Only occasionally, necrosis may be detected in either location (pancreatic or peripancreatic). Detection of infection in either situation is extremely important in the management of ANP. When imaging shows air in the necrosed area, it is suggestive of infection, which may be confirmed by percutaneous or endoscopic aspiration to detect the offending agent (bacteria or fungus). While many people may not agree with this approach, this is one way in which we can at least detect drug sensitivity of the infective organism.

The actual management starts with resuscitation with fluid therapy in order to stabilize circulatory volume, which is necessary for adequate organ perfusion including the pancreas. The amount of fluid to be given to achieve this can be substantial. It is stressed here that fluid sequestration in the third space in AP is akin to, as the time old teaching suggests, a third-degree burn. However, one should be judicious while being aggressive in fluid therapy so as to avoid pulmonary oedema and abdominal compartment syndrome [70]. The type of fluid to be used—normal saline, Ringer lactate or hydroxyethyl starch—is a contentious issue. Based on a review of the literature, there is no obvious advantage of the latter two [71, 72], and thus normal saline should continue to be used.

Next, one has to decide about the use of antibiotics. One has to be selective, because prophylactic antibiotic use does not prevent infection in sterile necrosis [73]. However, these should be used in patients with infected necrosis. The antibiotics to be used are based on the culture sensitivity of the material tested. Often, antifungal agents may have to be used.

The nutritional care of a patient with ANP is also an important issue. In the past, enteral feeding used to be thought to be harmful as it would stimulate the pancreas. In fact, early feeding has been shown to be beneficial, because it maintains the mucosal integrity and hence prevents bacterial translocation [74, 75]. Oral feeding is thus advised at the earliest. Even when patients do not take oral feeds, enteral feeding through a tube placed in the intestine needs to be encouraged and parenteral nutrition should be avoided.

Which nutritional formula—polymeric, monomeric (elemental) or oligomeric (semi-elemental)—to use is another issue. In a meta-analysis, it has been found that polymeric (standard formulation) is as effective as the other variants. It is far less costly than monomeric or oligomeric formulae [76]. Monomeric and oligomeric formulae have the advantage of less pancreatic stimulation as they have low fat content. Additionally, they contain free amino acids unlike polymeric diet which uses intact proteins. The advantage of free amino acids is that they bind with free trypsin in the gut and thus do not allow it to damage the pancreas [77].

The use of various supplements in enteral nutrition formulae like arginine, glutamine, omega 3 fatty acids, prebiotics and probiotics has not been shown to be of much benefit, and hence their routine use is not recommended [78].

Management of necrotic collections should next receive attention. Not all collections need active intervention, because most such collections are sterile and resolve spontaneously with time. Active intervention is required essentially for the control of infection. Intervention can be by surgery, interventional radiology or endoscopy.

Surgical necrosectomy is the oldest method. Unfortunately, it is associated with a high mortality and morbidity, including complications like bleeding, bowel fistula and pancreatic fistula. With the advent of minimally invasive approaches, the above problems have decreased. Minimally invasive techniques can be by laparoscopy or by step-up approach in which a drain is placed in the collection followed by necrosectomy by video-assisted retroperitoneal debridement (VARD). In a randomized trial, the step-up approach (PANTER trial) has been shown to be effective with lower mortality and fewer complications than open necrosectomy [79].

Using interventional radiology, drainage of a necrotic collection is achieved by percutaneous drainage, using a tube positioned inside the collection under ultrasound or CT guidance. The material aspirated is sent for culture. Once it is in place, the tube can be used to lavage the cavity with sterile normal saline usually thrice a day. With this approach, studies have shown success without further surgical intervention in 55.7% and 30% of infected necrosis [79, 80]. In the former report, the mortality was recorded to be 15.4%. If need be, the tract created to place the percutaneous tube can be used for necrosectomy. Intervention is deferred till such time that the necrosis is liquefied and separated from the inflamed tissue. It is usually 4 weeks from the onset of the disease. However, the exact timing of intervention is a debatable issue. Early drainage was associated with better outcome (less mortality and less organ failure) in one study [81]. In another study, however, timing has not been shown to have any effect on mortality or stay in the hospital [82].

Endoscopic drainage with or without necrosectomy is another minimally invasive procedure for the management of necrotic collections. The collection is drained by inserting a needle usually through the posterior wall of the stomach. Once inside the cavity, the needle is replaced with a plastic stent placed after dilating the tract. The same is used for lavage as for percutaneous drainage. More recently, direct endoscopic necrosectomy (DEN) has been described [83]. In this method, the tract is dilated, and an endoscope is introduced into the cavity to remove loose necrotic material, if need be, in multiple sittings. During irrigation, hydrogen peroxide (H_2O_2) can be used in place of normal saline. H_2O_2 separates the necrosed tissue better and facilitates its removal. Endoscopic necrosectomy has been shown to be associated with lower rates of organ failure and pancreatic fistula commonly observed after surgical necrosectomy [84]. To facilitate effective endoscopic drainage metallic stents have been introduced recently. The metal stents are either self-expanding, covered or lumen apposing ones [78, 85] and up to 90% resolution has been reported in one study with their use. One of the bothersome sequelae of ANP is disrupted pancreatic duct manifesting with prolonged collection or persistent pancreatic fistula. Identification at an early date helps in managing them better. Either ERCP or MRCP can be diagnostic. The former has the advantage in that it can be therapeutic also (pancreatic stent placement). The success of ERCP stent placement is dependent on whether the disruption is complete or incomplete. Incomplete disconnection can be stented successfully. Complete disruptions, on the other hand, are difficult to treat by ERCP. Even surgical treatment is hazardous though can be successful in some.

11.7 Reoperative Surgery for Failed Ileoanal Pouch

Currently ileal pouch–anal operation is the standard of care following total proctocolectomy for patients with ulcerative colitis and polyposis coli. This operation has excellent functional outcome with a good quality of life over the long term in both

adults and children [86, 87]. Unfortunately, this complex operation has a failure rate, usually resulting from anastomotic leak, leading to pelvic sepsis causing extensive fibrosis of the pelvic cavity with a non-distensible pouch. Removing the pouch and creating an ileostomy (permanent) is one way of managing such patients. This unfortunately affects the quality of the patients. The other option is to do a re-do procedure to salvage the pouch and thus avoid an ileostomy.

11.7.1 Type of Re-Do Surgery

Re-operative surgery can be either a re-operative procedure on the pouch itself with an intact ileal pouch–anal anastomosis or reconstruction of the pouch after dismantling the primary ileal pouch–anal anastomosis. The reconstruction for the second option can be done either by repairing the pouch or creating a new pouch and completing the procedure with a fresh ileal pouch–anal anastomosis [88].

11.7.2 Indications for Re-Do Surgery

Re-operative procedures are done either for septic complications resulting from an anastomotic leak or for strictures of the ileal pouch–anal anastomosis itself or that of the body of the pouch (including both the afferent and efferent limbs). Apart from these, a twisted pouch, an unduly long blind limb of the pouch or presence of a spur in the pouch will need revision surgery. A rare complication of a prolapsed pouch, too, needs re-operative surgery [89].

11.7.3 Evaluation of the Patient

All patients should have:

1. A thorough clinical examination including digital rectal examination and an examination under anaesthesia, if needed.
2. An endoscopy (pouchoscopy) must be done for adequate assessment of the pouch (presence of leak, spur, stricture, ulceration for which a biopsy to rule out Crohn's disease).
3. A CT or MRI should be done for the type of pouch, level at which the ileal pouch–anal anastomosis exists, presence of pelvic abscess, etc.
4. Anal manometry is desirable for the assessment of integrity of the anal sphincter.
5. Pouch defaecography can identify pouch dyssynergia.

11.7.4 Initial Management

Having assessed and decided to do another procedure, a diverting loop ileostomy should be done at least 6 months in advance. This will help control any anastomotic leak-related collection and pelvic sepsis. Patients with a pelvic abscess should have the abscess drained preferably through the anal canal and put on broad-spectrum antibiotics. All patients should initially receive non-surgical treatment for fistula, collection, abscess, localized stricture and spur in the pouch. If these do not succeed, then the re-operative surgery can be planned. Patients with pouch dyssynergia should be given a trial of biofeedback and pharmacotherapy as pelvic floor dyssynergia is difficult to treat and surgery is not rewarding [90].

11.7.5 Management of Specific Problem(s)

Leaking pouch: It is initially managed non-operatively by draining all collections through the transanal, transvaginal or percutaneous route. If it does not heal and the fistula is small, it can be closed surgically after removing all the infective material and fibrous tissue and mobilizing the pouch if required. If the leak is large (fistula), it may need dismantling the pouch before the fistula can be closed followed by re-anastomosing the same pouch (if suitable) or creating a fresh pouch for anastomosis. For a fresh anastomosis, a hand-sewn operation is done after carefully excising the rectal cuff. Stay sutures are then carefully placed before starting the anastomosis. If during mobilization the pouch is badly damaged, it is preferable to construct a new pouch if adequate ileum is available. Large pouch–vaginal fistulas are managed similarly. One should be mentally prepared to create an 'S' pouch, if the new pouch does not reach the anal canal.

Strictures causing obstructing symptoms commonly occur at the pouch–anal anastomosis site. Small localized strictures usually respond to anal dilatation. If, on the other hand, the stricture involves both the anal canal and the pouch, one has to do an operative correction. A stricturoplasty is often possible and should be done. Resection of the strictured segment is an option, in a difficult situation, provided vascularity of the segment is maintained. Other causes of obstructive symptoms are twist of the pouch and long efferent limb, causing kinking proximal to the pouch inlet. These are managed with suitable mobilization of the pouch, if possible. If not, the anastomosis can be revised with the original pouch or a fresh pouch. The same principle is applied for prolapse of the pouch with additional pouch fixation.

11.7.6 Approaches for Re-Do Surgery of the Pouch

The procedure(s) can be done either trans-abdominally or trans-anally. Except in patients with problems limited to the vicinity of the pouch (stricture, fistula, cuffitis, etc.), the operation is preferably done through the abdominal route.

The transabdominal approach involves a long midline incision. Upon entering the abdomen, all adhesions are released and the entire small bowel freed and kept aside. After taking due care of the bladder (in men) and uterus and ovaries (in women), one should remove all devitalized tissues and fibrous bands in the pelvis. The next step is location of the fistula. If possible, small fistula tracts can be excised and the resultant defect closed after confirming completeness of excision. For larger fistulous tracts, a careful examination of the pouch should be done and a decision taken whether the same pouch can be retained or another one constructed. The pouch is then taken down and the fistulous tract tackled. The pouch is the re-anastomosed with the anal canal. For the latter, the anal canal is opened just distal to the anastomosis. If needed, a small mucosectomy is done. The fresh anastomosis is almost always done by the hand-sewn technique. Having completed the anastomosis, a leak test is done (by water instillation technique) to rule out any leak. A drain is routinely placed, which is removed when the amount drained is minimal. The integrity of the anastomosis is ascertained a few weeks later by a water-soluble contrast enema study. The diverting stoma is closed only when the above test shows no leak of contrast, usually after 3 months of the operation.

11.7.7 Complications of Revisional/Reconstructive Pouch Surgery

This form of surgery has higher complications unlike the primary surgery. These include bleeding; anastomotic leak leading to pelvic collection and/or abscess; fistula formation; adhesive obstruction; and bowel, bladder and ureteric injury. In addition, stoma-related complications like prolapse or retraction can also occur.

11.7.8 Postoperative Complications

A large study comprising of over 500 patients who had re-do surgery found no mortality [90]. However, postoperative complications occurred in 53% of patients. Pelvic sepsis was the most common, occurring in 10% of patients. Other complications were anastomotic leak (8%), wound infection (8%), urinary injury (5%), haemorrhage (3%), anastomotic stricture (3%), fistula (3%), stoma complication (1%), bowel perforation (0.4%) and wound dehiscence (0.4%).

11.7.9 Quality of Life after Re-Do Pouch Surgery

The average daytime and night-time stool frequency in the above report were 6 and 2, respectively. Nearly half the patients used a pad after surgery for soiling. Over 30% patients had to modify their diet, and nearly 20% of patients had social and

vocational restrictions. Sexual problems were reported in another 20% of patients. In spite of these not too impressive outcomes, patients' satisfaction was reported to be high (90%). This is possibly related to the intense counselling these patients received before the operation. It is to be stressed here that a frank discussion with the patient providing all information is extremely important. The problems of re-do pouch surgery too needs to be highlighted. The projected expected results should be as realistic as possible. Failure rate too needs to be informed. Doing a diverting ileostomy 6 months before the re-do surgery gives the patient ample time to decide if they can adjust to the effects of the procedure or the patient could be offered a permanent ileostomy with or without removal of the pouch.

11.8 Predicting Postoperative Mortality in Cirrhotic Patients

Patients with cirrhosis are poor candidates for surgery, because of a high risk of mortality. This has necessitated a preoperative risk assessment in such patients. A number of predictive tools are available for this purpose. These include the Child-Turcotte-Pugh (CTP) score, the American Society of Anesthesiologists (ASA) class, Model for End Stage liver disease (MELD) score and the Mayo postoperative surgical risk score, which uses age and ASA class in addition to MELD score.

There are several reasons for patients with cirrhosis being at high risk for surgery:

1. Cirrhosis causes portal hypertension, progression of which is directly proportional to the degree of cirrhosis. Such patients can bleed and often bleed massively, following both hepatic and non-hepatic abdominal surgery. Apart from bleeding from collaterals, deficiency of thrombopoietin (synthesized by the normal liver) resulting in thrombocytopenia also causes bleeding. Hypersplenism, associated with cirrhosis, with reduced platelet number (due to sequestration) compounds the problem [91].
2. Patients with compromised liver function, following stress of surgery, often decompensate. This results in ascites, hepatic encephalopathy, hyperbilirubinaemia and raised international normalized ratio (INR).
3. In addition, hepatic resection in cirrhotics can cause postoperative liver failure due to loss of some of the functioning liver mass [92]. In addition, such patients do not tolerate well the stress of surgery, including general anaesthesia [93]. This happens even with non-hepatic surgery.
4. Most patients of cirrhosis are malnourished because of low protein synthesis. These patients have poor postoperative recovery due to poor wound healing [92], not uncommonly resulting in complete breakdown of the abdominal wound.
5. Cirrhotic patients have damaged Kupffer cells. These are important for cellular immunity. Hence, such patients have a higher risk of infection following an operation [92].

6. Patients with cirrhosis may have renal impairment with the potential to worsen following surgery leading to variable grades of renal dysfunction, which make fluid therapy extremely difficult [94].

11.8.1 Surgical Risk Assessment

Thus, patients with cirrhosis have a potential risk of both morbidity and mortality. Thus, risk assessment is important. However, it is inconsequential if an emergency operation has to be done to save the life of the patient when no non-surgical option is available, e.g. a ruptured aneurysm or a perforated intestine [95]. Risk assessment is reserved for elective procedures, where one has the opportunity to assess the risk before surgery. In doing so, one can identify a patient who has a contraindication for surgery and others who can have a relatively safe surgery.

The absolute contraindication to any elective procedure includes acute viral hepatitis, acute alcoholic hepatitis, severe chronic hepatitis, platelet count <40,000/cm, raised INR not correctable by various measures and cirrhosis associated with acute renal shut down, acute heart failure and severe pulmonary dysfunction [95].

The risk assessment scores used for evaluation of severity of liver disease include the following:

11.8.2 Child-Turcotte-Pugh (CTP) Score

It is the most conventional predictive tool used globally. It takes into account the following: ascites, serum albumin, serum bilirubin, encephalopathy and INR. Each of these parameters are given points [96]:

Ascites: 1. no ascites; 2. slight ascites; 3. moderate or severe ascites.

Albumin: 1. (serum albumin >3.5 g/dL); 2. (2.8–3.5 g/dL); 3. (<2.8 g/dL).

Bilirubin: 1 (serum bilirubin <2 mg/dL); 2. (2–3 mg/dL); 3. (>3 mg/dL).

INR: 1. (<1.7); 2. (INR 1.7–2.3); 3. (INR >2.3).

Encephalopathy: 1. (absent); 2. (grade 1–2); 3. (grade 3–4).

The total points are then counted. A score of 5–6 is labelled as CTP class A, 7–9 as CTP class B and count of 10–15 as CTP class C. CTP-A represents compensated cirrhosis, CTP-B represents compromised liver function and CTP-C represents decompensation. The A, B and C class of CTP have a 1- and 2-year survival of 100% and 85%, 80% and 60% and 45% and 35%, respectively [97].

CTP-A category patients can undergo surgery provided they do not have platelet deficiency and clinically significant portal hypertension. CTP-B category patients can be selectively chosen for surgery. And CTP-C patients have an absolute contraindication for surgery. CTP score has stood the test of time, but since some of the factors used in this scoring system such as ascites and encephalopathy are subjective, MELD is being increasingly used in its place.

11.8.3 ASA Classification

This is also one of the oldest patient evaluation tools for the assessment of risk following general anaesthesia and surgery. This measures a patient's overall health status, and it is not disease-specific. Nevertheless, it is still being used for risk stratification for surgery. The classification is as follows:

- Class 1. Normal healthy patient
- Class 2. Mild systemic disease
- Class 3. Severe systemic disease but not life-threatening
- Class 4. Severe systemic disease with constant life threat
- Class 5. Moribund and not likely to survive
- Class 6. Brain dead

Increasing ASA class has been reported to be associated with complications following surgery [98]. The complication rate is 2% in ASA 1, 5% in ASA 2, 14% in ASA 3, 37% in ASA 4 and 71% with ASA 5. The corresponding mortality rates were 0.02% for ASA 1, 0.14% for ASA 2, 1.41% for ASA 3, 11.14% ASA 4 and 50.87% with ASA 5.

Using ASA status and age along with MELD score, Teh et al. have shown good prediction of postoperative mortality [99].

11.8.4 Model for End-Stage Liver Disease (MELD) Score

This is currently the most commonly used predictive model. It was introduced nearly 20 years ago to predict mortality after transhepatic portosystemic shunt (TIPS). Subsequently, it has been used for organ allocation for liver transplantation. The score is based on three important laboratory parameters, namely, serum bilirubin, serum creatinine and INR. The score is calculated as:

$= 3.78 \times \log_e$ serum bilirubin (mg/dL)
$+ 11.2 \times \log_e$ INR
$+ 9.57 \times \log_e$ serum creatinine (mg/dL)
$+ 6.43$

MELD score has good correlation with CTP score; MELD score of <10 corresponds with CTP-A (compensated cirrhosis); MELD 11–15 corresponds with CTP-B (compromised liver function); and MELD >15 corresponds with CTP-C (decompensated cirrhosis) [94].

MELD scoring up to 11 has 5%–10% 90-day mortality, which rises to 25%–54% with MELD 12–25 reaching 90% with MELD >25.

11.8.5 Mayo Risk Score

It is another predictive model of postoperative mortality developed by researchers at the Mayo Clinic. It uses age and ASA class of the patient along with MELD score in cirrhotic patients. The score can be calculated online. ASA class V is the most accurate predictor of mortality at day 7 and MELD for mortality beyond 7 days. When age is added to the above, the predictability of postoperative mortality further rises [99].

11.8.6 MELD Na Score

Since the serum Na level is an important prognostic factor in patients with cirrhosis, it has been incorporated in the MELD score. MELD Na is calculated using the formula: MELD Na = MELD–Na–[0.025xMELDx(140–Na)] + 140.

Cho et al. [100] have evaluated MELD Na for the prediction of mortality and compared the results with CTP and MELD scores. They reported a 90-day mortality with CTP-A, -B and -C to be 2.1%, 22% and 54.5%, respectively. The same with MELD scores of 6–9, 10–14, 15–19, 20-24 and >25 was 3.5%, 8.9%, 14.3%, 22.5% and 63.6%, respectively. The corresponding figures for MELD Na are 1.9%, 6.2%, 13.2%, 20.6% and 50%. They also showed on multivariate analysis that ASA class ≥4, CTP ≥7, MELD ≥10 and MELD Na ≥10 are independent risk factors of a 90-day mortality following surgery in patients with cirrhosis.

While no single model offering the most accurate prediction, Mayo risk score and MELD Na score promises are good indicators. These need to be validated in multicentre studies.

11.9 Colorectal Surgery: With or Without Bowel Preparation?

This issue is frequently debated. Conventionally, patients for colorectal surgery receive mechanical bowel preparation (MBP) with or without oral antibiotics. This is aimed at reducing infective complications associated with colorectal surgery. It was Poth who in 1982 reported that the majority of patients (90%) surviving colorectal surgery had surgical site infection [101]. Even before that, Nichols et al. had shown reduced surgical site infection (SSI) rate using a combination of mechanical bowel preparation and oral neomycin and erythromycin—a strategy commonly practiced even today all over the world. They reported reduction in SSI from 43% to 9% [102].

In spite of these observations, a number of studies raised doubts about the utility of MBP or antibiotic bowel preparation (ABP) [103–105]. Some have suggested the use of ABP alone without the need of MBP [106]. These studies essentially have shown no difference in results with or without MBP [103–105]. One study has shown better results with ABP alone [106]. To compound the issue further, patients receiving ABP have been shown to have a higher rate of *Clostridium difficile* infection [107].

However, a large number of colorectal surgeons still use MBP and/or ABP as revealed in a series of surveys conducted by the American Society of Colon and Rectal Surgeons (Table 11.1).

From the table, it is clear that surgeons are gradually moving away from bowel preparation for colorectal surgery but they have not given it up altogether.

In the light of the discussion so far, one has to seriously consider the results of the American College of Surgeons National Surgical Quality Improvement Programme database with reference to bowel preparation for colorectal surgery. This is a robust data set analysed with diligence and exhaustive statistical evaluation [113]. The authors of this study included 27,804 eligible patients from a cohort of 64,357 patients. This is a case control study. They reported bowel preparation in 5417 cases (23.5%), ABP in 1374 (5.9%) cases and MBP and ABP in 8855 (38.0%).

Comparative results of SSI in the various groups revealed (as compared to no preparation) patients with MBP and ABP had less SSI (odds ratio 0.39, $p < 0.001$), deep site infection (odds ratio 0.56, $p < 0.001$), anastomotic leak (odds ratio 0.53, $p < 0.001$), *Clostridium difficile* infection (odds ratio 0.53, $p = 0.35$) and unscheduled postoperative re-exploration (odds ratio 0.79, $p < 0.001$). Hospital stay, too, has been shown to be shorter in the bowel preparation groups ($p < 0.001$).

Similarly, those receiving ABP, as compared to no preparation, had better results in terms of the above complications, except for *Clostridium difficile* infection, unscheduled re-exploration and wound dehiscence, which were not statistically different from the no preparation group.

When ABP and MBP were compared with dual preparation (ABP + MBP), ABP alone or MBP alone had higher SSI compared to dual preparation (odds ratio 1.61, $p = 0.002$). Anastomotic leak was higher with MBP alone than dual preparation (odds ratio = 1.60, $p < 0.001$).

The impact of these modes of bowel preparation was evaluated separately for colon and rectal surgery. For colonic surgery, again the benefits of ABP and MBP were seen with less SSI, deep site infection, anastomotic leak, wound dehiscence,

Table 11.1 Results of surveys of colorectal surgeons regarding bowel preparation

Author, year	Mechanical bowel preparation	Antibiotic bowel preparation
Beck and Fazio, 1990 [108]	100%	87%
Nichols, 1997 [109]	100%	88.5%
Zmora, 2003 [110]	99%	75%
Market, 2010 [111]	76%	36%
Beck and McCoy, 2016 [112]	59%	48%

Clostridium difficile infection or unscheduled reoperation than in patients with no bowel preparation. Even ABP alone had significantly less SSI, deep site infection and *Clostridium difficile* infection. However, ABP alone did not show significantly different anastomotic leak wound dehiscence or re-exploration rates. The hospital stay following colonic surgery was significantly reduced with all forms of bowel preparation (ABP, MBP or dual bowel preparation) as compared to no bowel preparation.

As for rectal surgery, both MBP and ABP showed significantly lower SSI, deep site infection, wound dehiscence, *Clostridium difficile* infection and unscheduled re-exploration. ABP alone did not lower *Clostridium difficile* infection than no bowel preparation. Dual bowel preparation had lower reoperation rate than no preparation, but hospital stay with dual bowel preparation was not better than no preparation.

Thus, it seems reasonable to advocate both MBP and ABP while undertaking colon and rectal surgery. This finds support in a statement made by Frontali and Panis in an editorial commentary where they stated "there is lot of evidence suggesting that MBP +OA [oral antibiotics] should be the gold standard for colorectal surgery" [114].

11.10 Stepwise Assessment of Patients with Haematochezia

Haematochezia, by definition, refers to the passage of red blood per rectum. It is a common condition occurring in about 15% of adults [115]. Often these patients require hospitalization for blood transfusion, upper/lower gastrointestinal (g.i.) endoscopy (or both) and/or radiological studies. All these add to the expenses. It is responsible for an annual hospital admission rate of 21/100,000 in the USA with an annual healthcare cost of US$ 5 billion [116]. Thus, it is imperative for everyone involved in the care of these patients to know how to assess and manage these patients. Haematochezia can occur from any part of the alimentary tract starting from the oesophagus to the anorectal area. Bleeding from the lower g.i. tract (colon and rectum) is the common cause of haematochezia, but an upper g.i. source (oesophagus, stomach and duodenum) can also cause haematochezia in up to 15% of cases [117].

When a patient comes to the hospital with haematochezia, one should proceed in a stepwise manner starting with:

11.10.1 Step 1

Stabilization of the patient. Look for signs of haemodynamic instability (tachycardia, hypotension). If present, resuscitation with fluid therapy must be started. Depending on the response, drug therapy should be considered (inotropes).

Simultaneously, a quick estimation of the haemoglobin level should be done. If the haemoglobin is low, blood transfusion (packed red blood cell) must be arranged. The amount of blood to be transfused varies, but current evidence suggests a target haemoglobin of >7 g/dL is adequate in most patients [118]. If the platelet count is <50,000/dL, then platelets will also need to be transfused [118]. If patients are on anticoagulation for any reason, it should be stopped and/or its effects reversed.

11.10.2 Step 2

Assessment of the type of bleeding. It is useful to look at the colour of the blood. If bright red, it indicates a more distal source of bleeding. On the other hand, if it is maroon, the bleeding is more proximal in origin. The amount of blood passed should also be assessed as it indicates the site of bleeding, e.g. small amount of bleeding occurring as a drop or smearing the stool indicates a rectal source. Conversely, haematochezia from gastro-oesophageal, colonic and small bowel is sufficiently large to cause haemodynamic instability. A large number of patients with lower g.i. bleeding do not have hypotension, which occurs in only 2% of patients [119]. The simplest way to ascertain whether a person is bleeding from an upper g.i. source is to pass a nasogastric tube and aspirate the contents. However, a recent study has negated its usefulness in establishing the source of bleeding [120]. Mortensen et al. have shown that blood urea and creatine ratio of 30:1 is a marker of upper g.i. bleeding [121]. It is also useful to proceed with risk stratification of the individual patient. There are a number of tools for this and include the Rockall score [122], AIMS 65 score [123, 124], Glasgow–Blatchford score [123, 124] and Forrest classification.

Rockall score [122]. This was initially developed to identify patients of acute upper g.i. bleeding who are likely to have an adverse outcome. Later, it was used for the prediction of mortality. It uses five variables: age, presence of shock, presence of comorbidity, specific diagnosis and evidence of bleeding. The scoring is as follows:

Variable	Score 0	Score 1	Score 2	Score 3
(A) Age.	<60 years	60–79 years	>80 years	–
(B) Shock	Absent	Pulse >100 min; systolic blood pressure >100 mmHg	Systolic blood pressure <100 mmHg	–
(C) Comorbidity	None	–	Heart failure, ischaemic heart disease	Renal or liver failure
(D) Diagnosis	Mallory–Weiss	All other conditions	GI malignancy	Metastatic cancer
(E) Evidence of bleeding on endoscopy	None	Presence of blood, adherent clot, spurting vessel	–	–

All the above scores are summed up for a total score, which if <3 indicates a good prognosis and if >8 indicates a high risk of mortality.

Glasgow–Blatchford score (GBS). This is aimed at identifying a patient with upper g.i. bleeding who will need blood transfusion and/or an upper g.i. endoscopy. This tool takes six characteristics into consideration. These are haemoglobin level, urea level, presence of melena or syncopal attack and absence of liver or heart disease either in the past or the present. The scoring is as follows:

Parameters	Score	
	Men	Women
(1) Haemoglobin g/dL		
12–12.9	1	–
10–11.9	3	1
<10	6	6
(2) Blood urea mol/L		
6.5–8.0	2	2
8.0–10.0	3	3
10.0–25.0	4	4
(3) Blood pressure (mmHg)		
100–109	1	1
90–99	2	2
<90	3	3
(4) Pulse ≥100/min	1	1
(5) Melena	1	1
(6) Syncope	2	2
(7) Liver disease	2	2
(8) Heart failure	2	2

Note: Score '0' is reserved in the presence of all of the following: haemoglobin >12.9 g/dL in men or >11.9 g/dL in women, blood urea <6.5 mg/dL, blood pressure >109 mmHg, pulse <100/min, no melena/syncope, no heart failure

When the total score exceeds 6, it indicates a higher risk, which needs definitive therapy. Nearly 25% of patients with upper g.i. bleeding have a score of '0'. All these patients survive the bleeding episodes without any intervention and are suitable for outpatient treatment [123].

AIMS 65 score [124]. This score was developed for the prediction of mortality in patients with acute upper g.i. bleeding. This is a clinical score easily calculated on the bedside. Each letter of AIMS 65 stands for a risk factor with equal weightage. The sum of scores of all the factors reflects severity of the episode. The factors are:

A = Albumin <3.0 g/dL	No	0 point
	Yes	1 point
I = INR >1.5	No	0 point
	Yes	1 point
M = Altered mental status (Glasgow coma scale <14)	No	0 point
	Yes	1 point
S = Systolic blood pressure ≤90 mmHg	No	0 point
	Yes	1 point
≥65 years of age	No	0 point
	Yes	1 point

Zero points have 0.3% mortality; patients with higher score have increased hospital stay. Albumin level was found to be the most important predictor of mortality.

Forrest classification. This is used essentially for the selection of patients for endoscopic treatment [125]. The classification is as under:

Acute haemorrhage

- Ia: spurting vessel
- Ib: oozing vessel

Signs of recent haemorrhage

- IIa: non-bleeding visible vessel
- IIb: adherent clot
- IIc: flat pigmentation on ulcer bed

Lesions without active bleeding

- III: no sign of recent haemorrhage or fibrin covered ulcer bed

This classification categorises patients of upper g.i. bleeding into a high and low risk of mortality. It is commonly used for endoscopic evaluation and management.

PNED score. An Italian scoring system has also been introduced: PNED (Progetto Nazionale Emorragia Digestiva). The scores are as follows:

Score			
1	2	3	4
Risk factors ASA 3, time to admission <8 h	Haemoglobin<7 g/dL Age >80 years Renal failure	Rebleeding ASA 4 Neoplasia Liver cirrhosis	Failure of endoscopic treatment

Cumulative score was then used for low risk (score ≤4) and medium risk (score >8). Marmo et al. through a prospective study validated the predictive value of this scoring system. They also compared their result with Rockall score and showed it to be better than the latter.

T score: It is a recent scoring system described. It is simple, and yet it can predict an accurate high-risk stigmata and active bleeding. It uses pre-endoscopic clinical and laboratory data and uses the following four variables: general condition, heart rate, systolic blood pressure and haemoglobin level. The values of each are as under:

Variable	1	2	3
General condition	Poor	Intermediate	Good
Pulse rate per minute	>110	90–100	<90
Systolic blood pressure (mmHg)	<90	90–110	>110
Haemoglobin level (g/dL)	≤8	9–10	>10

T score is the summative value of all four parameters. Less than 6 is T_1 (high risk), 7–9 is T_2 (moderate risk) and value of 10 is T_3 (low risk).

The authors of this scoring system have suggested that the T score can predict high-risk endoscopic stigmata, rebleeding and mortality as accurately as the Glasgow–Blatchford score [126].

11.10.3 Step 3

This requires an evaluation of the cause based on the presence or absence of pain either in the abdomen or pelvis. This is usually evident from the history. Conditions presenting with haematochezia without pain can be due to diverticular disease, carcinoma rectum, vascular malformations and haemorrhoids. Massive upper g.i. bleeding, e.g. from ruptured oesophageal varices, can also have painless haematochezia. Painful haematochezia can be due to radiation proctitis, ischaemic bowel disease, inflammatory bowel disease or infective colitis. Ischaemic bowel disease should be considered in elderly patients who can present with haematochezia associated with pain.

Typically, such patients experience abdominal pain before haematochezia. Not infrequently, these patients have episodes of hypotension (syncopal attacks). When patients present with severe acute central abdominal pain, abdominal tenderness, associated with hypotension and haematochezia, a diagnosis of acute mesenteric ischaemia should be considered. Patients with inflammatory bowel disease frequently give history of chronic abdominal pain, diarrhoea with or without blood, general fatigue not infrequently with associated complications like colonic stricture, malignancy or perianal disease. Painful passage of blood can also be due to solitary rectal ulcer syndrome and fissure in ano. However, the quantity of blood passed in these latter conditions is usually small in amount. Apart from abdominal examination, rectal examination too must be done. This will exclude perianal diseases. Digital rectal examination easily detects malignancies of the anorectum, stricture (as in Crohn's disease) or lax sphincter (as in pelvic descent with resultant prolapse), causing solitary rectal ulcer.

11.10.4 Step 4

Endoscopic evaluation: This is an important step in evaluating patients of haematochezia. For patients presenting with hypotension (commonly due to upper g.i. bleeding), they should have an emergency upper g.i. endoscopy to detect the source. If unrewarding, a colonoscopy should be done. Whether colonoscopy should be done early or not is not clear, because most patients of haematochezia due to lower g.i. causes stop bleeding spontaneously. However, early colonoscopy can show signs of recent bleeding, which can often be treated endoscopically. Early colonoscopy, however, has not shown any impact on transfusion rate, rebleeding rate, hospital stay or mortality [118].

11.10.5 Step 5

Rule out bleeding source from small bowel: This is important, because the small bowel can be the source of g.i. bleeding in 5%–10% of patients [127]. Bleeding from small bowel should be suspected when both upper g.i. and lower g.i. endoscopies are unproductive. The lesions of the small bowel which bleed vary according to age. In young patients, the common cause is Meckel's diverticulum. Middle-aged patients are more likely to have vascular malformation, small bowel tumours (especially gastrointestinal stromal tumours; GIST) and Crohn's disease. Elderly patients have arteriovenous malformation and vascular tumours of the small bowel.

Investigations to detect these lesions largely depend on whether the patient is haemodynamicably stable or not. If unstable, an emergency angiography is done to detect the lesion and embolise the bleeding vessel [128]. Patients who are stable should undergo CT angiography and embolization if bleeding continues [129]. Bleeding from the small bowel often occurs slowly, and hence patients commonly have melena rather than haematochezia. For slow bleeders, capsule endoscopy is preferred, provided there is no evidence of the past/present episodes of bowel obstruction [128]. Radioisotope scan using Tc^{99m} labelled RBC can detect bleeding from Meckel's diverticulum or other slow bleeding conditions [128].

11.11 Resection Versus Radiofrequency Ablation for Very Early-Stage Hepatocellular Carcinoma

An effective surveillance strategy for patients with chronic liver disease has resulted in the detection of hepatocellular carcinoma (HCC) at a very early stage. Much of it is due to better imaging methods currently being used. The best method to treat these patients is debated. Most reports are based on retrospective data comprising a small number of patients. Patients with these very small tumours, irrespective of the

type of treatment, are likely to live really long. Therefore, long-term follow-up is needed. Unfortunately, in these reports, follow-up has been only 28–58 months [130–133]. Wang et al. retrospectively analysed their data using resection in 52 and radiofrequency ablation (RFA) in 92 patients. Their median follow-up was only 28.8 month. They showed an identical overall survival but better recurrence-free survival in the RFA group [130]. With an almost similar number of patients (resection in 50 and RFA in 66 patients), Hung reported similar overall and recurrence-free survival in their retrospective data with 42.1 months of follow-up [131]. Pompili et al. also reported a similar overall and recurrence-free survival and a follow-up of 34 months. They included 99 patients for resection and 109 patients for RFA [132]. Peng et al. and Liu et al. followed their patients after surgery or resection for longer durations (58.3 months and 43.5 months, respectively). While Peng et al. reported better overall survival with RFA but the same recurrence-free survival in the two groups [134], Liu et al. reported equal overall survival rates in the two groups [133]. Recurrence-free survival was better in the surgical resection group in this report. More importantly, better overall and recurrence-free survival was noted on propensity score match analysis in the surgical resected group in this study [133]. Even randomized trials which selected tumours <3 cm for resection or RFA reported variable results [134–136]. However, these studies did not include patients with tumours <2 cm.

Against this background, it is worthwhile to consider an article form Korea published in *Liver International* [137]. It is a retrospective study from a high-volume centre. They have analysed the results of resection (631 patients) and RFA (577 patients) treated over a period of 13 years. They have followed these patients after treatment for >7 years. They have included very early-stage HCC measuring ≤2 cm with child's A status and performance status ECOG 0, without microvascular invasion or metastases. They did a propensity score analysis for estimation of 15-year overall survival rates. With propensity score analysis, they reported survival rates of 60.4% with surgery vs 51.6% with RFA. The difference was statistically significant. Recurrence-free survival rates too were significantly better with surgery (resection) vs RFA (37% vs 23.6%; $p < 0.001$). Year-wise survival was shown to be 99%, 94.8%, 89.5%, 60.2% and 63% at 1, 3, 5, 10 and 15 years, respectively, in the resection group. Corresponding figures in the RFA group were 98.8%, 89.9%, 80%, 59.1% and 46.2%. Obviously with a large study population and long-term follow-up, this paper is likely to have a major influence on the treatment of very small early-stage HCC.

11.12 An Update on Hepatocellular Adenoma

Hepatocellular adenoma (HA) is an uncommon benign tumour of the liver. Women in their reproductive life are commonly affected by this tumour, especially those who use oestrogen-rich oral contraceptives. This is not to suggest that men are immune to this tumour. Men with history of androgen therapy, glycogen storage

disease, maturity-onset diabetes of youth and metabolic syndrome have all been reported to develop HA [138]. They are benign and remain largely so—asymptomatic in most instances and are incidentally discovered. This statement notwithstanding, these tumours are notorious for their behaviour—first, they are known to bleed and rupture, and second, they have the potential to develop malignancy. These two facts have attracted the attention of surgeons and others involved in the management of these tumours.

11.12.1 Risk Factors for Development of HA

The association between HA in women on oral contraceptive use has been known for nearly 50 years [139]. This association has been related to the duration and dose of the drug used [140]. These tumours can regress following the discontinuation of the oral contraceptive pill; this proves their association. The presently used OCPs have less oestrogen content and have a lower incidence of the disease [141], suggesting an association with the dose of oestrogen.

The tumours are less frequent in men. However, they have a strong association with sex hormones, such as anabolic androgenic steroid used in Fanconi anaemia. The association has also been seen in men with elevated endogenous androgen [142].

Other factors associated with HA are glycogen storage disease type I and III, familial adenomatous polyposis (FAP), primary sclerosing cholangitis (PSC), obesity, alcoholism, Klinefelter syndrome and maturity-onset diabetes of youth, type III (MODY3). The last one is seen in the familial form of hepatic adenomatosis (when more than 10 HA are present) [143]. HA are essentially a disease of a non-cirrhotic liver. However, recently these tumours are being reported to develop in alcoholic cirrhotics too [144].

11.12.2 Modern Classification of HA

These are traditionally considered homogeneous tumours. This concept has changed now. Based on molecular characteristics, these are now classified as:

(a) HNF (hepatocyte nuclear factor)-1α (HNF1α) mutated
(b) β-catenin mutated
(c) Inflammatory type
(d) Unclassified without gene mutation

β-catenin mutated tumours are divided further into

- With exon 3 mutation
- With exon 7/8 mutation [145]

The unclassified tumour has a distinct subtype, which has recently been shown with activation of the sonic hedgehog pathway secondary to overexpression of GLI family zinc finger 1 (GLI1), also known as glioma-associated oncongene [145].

11.12.3 Characteristics of Various HA

HNF1α tumours occur as a result of mutation of the tumour suppressor gene transcription factor 1 (TCF1), which encodes hepatocyte nuclear factor 1 (HNF1) expressed in tissues including liver.

HNF1α is important for hepatocyte differentiation for expression of various liver-related genes. Its inactivation results in tumourigenesis (HA) through a complex mechanism. These tumours are common, comprising 30–50% of all cases. They are associated with maturity-onset diabetes of the youth type 3 (MODY3) and hepatic adenomatosis. These tumours have the least rates of bleeding and malignancy. Pathologically, they have a variable degree of steatosis. However, on immunohistochemistry, they lack the expression of L-fatty acid-binding protein (L-FABP).

Inflammatory type of HA (IHCA) is the most common type (40%–55%). These develop due to the activation of signal transcription 3 (STAT3) signalling pathways. As a result of this, an acute inflammatory response occurs in tumoural hepatocytes due to mutation of interleukin 6 signal transducer gene (IL6ST). Once activated, IL6 induces STAT3 signalling. Not all adenomas of this type have the IL6ST gene. However, STAT 3 activation and expression of GP130 protein are seen in some IHCA for unknown reasons. The simultaneous presence of β-catenin mutation can also be seen in some cases, which explains why some inflammatory HAs undergo malignancy. The other real danger of these tumours is that they have a high incidence of rupture and bleeding.

Pathologically these tumours are characterized by thickened blood vessels (arteries), dilatation of the sinusoids and steatosis. On immunohistochemistry, C-reactive protein and serum amyloid staining can be seen. Tumoural hepatocytes can be positive for liver-type fatty acid-binding protein (LFABP) staining on immunohistochemistry. Those IHCAs having mutation of β-catenin have positive nuclear staining for β catenin.

β-catenin mutated tumours are relatively less common accounting for 10%–18% of cases. They occur due to mutation of β-catenin gene leading to development of HA. Macroscopically, they are well defined tumours with fleshy appearance on cut section. Microscopically no definite characteristic is noted excepting columns of hepatocytes interspersed with arteries. Pseudoacinar formation can be seen in some. They do not show steatosis. However, nuclear staining for β-catenin is universal, even though the same may be patchy. Since glutamyl synthetase is a marker of β-catenin, it can be detected in the cytoplasm and immunohistochemistry. These tumours have maximum malignant potential, which develops in 5%–10% of cases [145].

Unclassified hepatic adenomas are the least common form of hepatic adenomas. No genetic abnormalities are found in these tumours. Neither do they have any characteristic pathological feature. Some of these tumours may have necrosis and haemorrhage inside the tumour, which can mimic hepatocellular carcinoma which needs to be ruled out. Moreover, some unclassified HA (with sonic hedgehog activation) have a higher risk of bleeding [145].

11.12.4 Imaging of HA

Ultrasonography (US), computerized tomography (CT) and magnetic resonance imaging (MRI) have all been used in the diagnosis. Since US has only 30% sensitivity, CT and MRI are commonly used. However, contrast-enhanced US (CEUS) has been shown to have some role. In addition to these, nuclear scan is also described.

US: HA can be iso-/hypo-/hyperechoic, and hence it is not possible to differentiate HA from other lesions. CEUS using sulphur hexafluoride has been introduced to enhance these lesions better. This has been reported to correctly diagnose HA in 80% of patients [146]. In another report, CEUS has been shown to demonstrate enhancement pattern of HA similar to that of CT and MRI [147]. Nonetheless, these reports are not universally replicated. Thus, as of now, US should be used to screen hepatic lesions. Once detected, these should have a CT and/or MRI.

CT: As with US, CT scan can also detect incidental HA during scanning for other purposes. Incidentally discovered HA on CT scan should be evaluated further by multiphasic CT for appropriate characterization of these lesions. A triple-phase CT scan is obtained first in non-contrast phase, followed by arterial phase after 30 s of intravenous contrast injection and lastly by a portal venous phase after 60–80 s [148]. HA has homogenous enhancement in the arterial phase. However, this feature is seen in other conditions, like HCC, vascular metastases as in neuroendocrine tumour and focal nodular hyperplasia. In the portal venous phase, HA is isoattenuating like the surrounding liver, because it also contains hepatocytes [148]. The presence of haemorrhage can be seen with increased enhancement. HA on CT scan have a well-defined border without lobulation and in about in about one-quarter of patients low-enhancing pseudocapsule. Calcifications too can be frequently seen [148].

MRI: The majority of HA are hyper- or iso-intense with reference to the liver in T_1-weighted images. The hyperintensity is related to presence of fat. It may be due to intralesional bleeding also [149]. The presence of fat can be confirmed with chemical-shift imaging with loss of signal; since HCCs also have fat in a number of cases (40%), it is difficult to differentiate the two [148]. Hyperintense lesions on T_1-weighted image can also be seen in certain metastatic liver diseases notably melanoma and in cysts with high-protein content [148]. On T_2-weighted images, HA tends to be slightly hyperintense. However, this finding too is shared by other lesions like HCC and metastatic lesions. Heterogeneity of a lesion is present in 50% of HA in either T_1- or T_2-weighted images. HA in some cases shows peripheral rim

enhancement—low signal intensity in T_1- and variable intensity T_2-weighted images. On contrast-enhanced MRI using gadolinium, these lesions become hyperintense in the arterial phase.

A central scar is never seen in HA [148]. Thus, it is not possible to differentiate HA from focal nodular hyperplasia, hepatocellular carcinoma and vascular metastases by T_1- and T_2-weighted images in MRI. To improve upon this, the use of superparamagnetic iron oxide (ferumoxide) and mangafodipir trisodium have been suggested. Ferumoxide is taken up by the Kupffer cells (KC) and hence detected in FNH (which has abundant KC) with reduced signal intensity on T_2-weighted imaging [150]. Mangafodipir trisodium is a dye, which is taken up by hepatocytes when injected. It is then excreted in the bile. Hence, hepatocyte-containing lesions, like HCC, HA and FNH, enhance with this dye. Lesions which have no hepatocytes (metastasis and vascular malformations) fail to enhance. Other developments in MR imaging of hepatic lesions are MR elastography and conspicuity analysis before and after gadolinium injection. However, the results of these studies need to be validated in prospective large studies [151]. One should also take the clinical characteristics into consideration for reasonable accuracy of diagnosis. This is exemplified below:

1. Healthy young women in reproductive age with history of long-term use of OCPs are likely to have HA.
2. Men with history of anabolic steroid use or glycogen storage disease and haemochromatosis are likely to have HA.
3. Patients with cirrhosis with a liver mass associated with raised alphafetoprotein are likely to have HCC.
4. Patients with liver lesion and prior history of untreated primary tumour elsewhere are likely to have metastatic liver tumour.

Nuclear scans: A number of radioisotopes have been used in the evaluation of liver tumours. These include gallium 67, sulphur colloid, technetium and 18 fluorodeoxyglucose (18FDG). Benign tumours like HA do not take up gallium unlike HCC, which can show higher uptake of the molecule [148]. Both HCC and HA do not show uptake on sulphur colloid scan, because neither of them contains KC, which take it up. This is unlike FNH, which takes up sulphur colloid, because this tumour has plenty of KC [148]. On hepatobiliary iminodiacetic acid (HIDA) scan, HA shows uptake, because it is composed of hepatocytes, but the nucleotide cannot be excreted as HA does not have a bile duct. As a result, HA shows retention of the isotope (so-called hot nodule); FDG uptake is not seen in benign tumours like HA [148]. A combination of radioisotope scans can be confirmatory of the diagnosis of HA, if the lesion does not show uptake on gallium or sulphur colloid scan but shows increased uptake on HIDA scan.

Treatment strategy: HA are at risk of haemorrhage and malignant transformation and hence should be removed surgically [152]. The risk of bleeding can be as high as 30%–50% and appears to be related to size. Therefore, larger tumours (>5 cm) should be removed to prevent life-threatening risk of bleeding that these patients have to live with. Symptomatic patients should certainly have it done. Asymptomatic patients, especially those with <5 cm HA, can remain on regular follow-up. If the

lesion increases in size or the patient becomes symptomatic, surgical removal is the option. The above risks of HA are quite high in men, and hence surgical treatment has been advocated even when the tumour is small [149]. In women, even though tumours can regress on withdrawal of OCP, the risk of malignant transformation remains, and hence it is better to remove them [149]. The same strategy is advocated for HA-B type tumours in women above 50 years or below 15 years, because these tumours may represent well-differentiated HCC [153]. A non-surgical approach using radiofrequency ablation and transarterial embolization can be used. Being less invasive, these modalities have become attractive options.

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